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(54) Title: **MAMMALIAN EXPRESSION SYSTEMS FOR HCV PROTEINS**

(57) Abstract

Mammalian expression systems for the production of HCV proteins. Such expression systems provide high yields of HCV proteins, and enable the development of diagnostic and therapeutic reagents which contain glycosylated structural antigens and also allow for the isolation of the HCV etiological agent.

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MAMMALIAN EXPRESSION SYSTEMS FOR HCV PROTEINS

Background of the Invention

5 This invention relates generally to Hepatitis C Virus (HCV), and more particularly, relates to mammalian expression systems capable of generating HCV proteins and uses of these proteins.

10 Descriptions of Hepatitis diseases causing jaundice and icterus have been known to man since antiquity. Viral hepatitis is now known to include a group of viral agents with distinctive viral organization protein structure and mode of replication, causing hepatitis with different degrees of severity of hepatic damage through different routes of transmission. Acute viral hepatitis is clinically diagnosed by well-defined patient symptoms including jaundice, hepatic tenderness and an elevated level of liver transaminases such as Aspartate Transaminase and Alanine Transaminase.

15 Serological assays currently are employed to further distinguish between Hepatitis-A and Hepatitis-B. Non-A Non-B Hepatitis (NANBH) is a term first used in 1975 that described cases of post-transfusion hepatitis not caused by either Hepatitis A Virus or Hepatitis B Virus. Feinstone et al., New Engl. J. Med., 292:454-457 (1975). The diagnosis of NANBH has been made primarily by 20 means of exclusion on the basis of serological analysis for the presence of Hepatitis A and Hepatitis B. NANBH is responsible for about 90% of the cases of post-transfusion hepatitis. Hollinger et al. in N. R. Rose et al., eds., Manual of Clinical Immunology, American Society for Microbiology, Washington, D. C., 558-572 (1986).

25 Attempts to identify the NANBH virus by virtue of genomic similarity to one of the known hepatitis viruses have failed thus far, suggesting that NANBH has a distinctive genomic organization and structure. Fowler et al., J. Med. Virol. 12:205-213 (1983), and Weiner et al., J. Med. Virol. 21:239-247 (1987). Progress in developing assays to detect antibodies specific for NANBH has been 30 hampered by difficulties encountered in identifying antigens associated with the virus. Wards et al., U. S. Patent No. 4,870,076; Wards et al., Proc. Natl. Acad. Sci. 83:6608-6612 (1986); Ohori et al., J. Med. Virol. 12:161-178 (1983); Bradly et al., Proc. Natl. Acad. Sci. 84:6277-6281 (1987); Akatsuka et al., J. Med. Virol. 20:43-56 (1986).

35 In May of 1988, a collaborative effort of Chiron Corporation with the Centers for Disease Control resulted in the identification of a putative NANB agent, Hepatitis C Virus (HCV). M. Houghton et al. cloned and expressed in E. coli a NANB

agent obtained from the infectious plasma of a chimp. Cuo et al., Science 244:359-361 (1989); Choo et al., Science 244:362-364 (1989). CDNA sequences from HCV were identified which encode antigens that react immunologically with antibodies present in a majority of the patients clinically diagnosed with NANBH.

5 Based on the information available and on the molecular structure of HCV, the genetic makeup of the virus consists of single stranded linear RNA (positive strand) of molecular weight approximately 9.5 kb, and possessing one continuous translational open reading frame. J. A. Cuthbert, Amer. J. Med. Sci. 299:346-355 (1990). It is a small enveloped virus resembling the Flaviviruses. Investigators

10 have made attempts to identify the NANB agent by ultrastructural changes in hepatocytes in infected individuals. H. Gupta, Liver 8:111-115 (1988); D.W. Bradly J. Virol. Methods 10:307-319 (1985). Similar ultrastructural changes in hepatocytes as well as PCR amplified HCV RNA sequences have been detected in NANBH patients as well as in chimps experimentally infected with infectious HCV

15 plasma. T. Shimizu et al., Proc. Natl. Acad. Sci. 87:6441-6444 (1990).

Considerable serological evidence has been found to implicate HCV as the etiological agent for post-transfusion NANBH. H. Alter et al., N. Eng. J. Med. 321:1494-1500 (1989); Estaben et al., The Lancet: Aug. 5:294-296 (1989); C. Van Der Poel et al., The Lancet Aug. 5:297-298 (1989); G. Sbolli, J. Med. Virol. 20 30:230-232 (1990); M. Makris et al., The Lancet 335:1117-1119 (1990). Although the detection of HCV antibodies eliminates 70 to 80% of NANBH infected blood from the blood supply system, the antibodies apparently are readily detected during the chronic state of the disease, while only 60% of the samples from the acute NANBH stage are HCV antibody positive. H. Alter et al., New Eng. J. Med. 25 321:1994-1500 (1989). The prolonged interval between exposure to HCV and antibody detection, and the lack of adequate information regarding the profile of immune response to various structural and non-structural proteins raises questions regarding the infectious state of the patient in the latent and antibody negative phase during NANBH infection.

30 Since discovery of the putative HCV etiological agent as discussed supra, investigators have attempted to express the putative HCV proteins in human expression systems and also to isolate the virus. To date, no report has been published in which HCV has been expressed efficiently in mammalian expression systems, and the virus has not been propagated in tissue culture systems.

35 Therefore, there is a need for the development of assay reagents and assay systems to identify acute infection and viremia which may be present, and not currently detected by commercially-available assays. These tools are needed to

help distinguish between acute and persistent, on-going and/or chronic infection from those likely to be resolved, and to define the prognostic course of NANBH infection, in order to develop preventive and/or therapeutic strategies. Also, the expression systems that allow for secretion of these glycosylated antigens would be 5 helpful to purify and manufacture diagnostic and therapeutic reagents.

Summary Of The Invention

This invention provides novel mammalian expression systems that are capable of generating high levels of expressed proteins of HCV. In particular, full-10 length structural fragments of HCV are expressed as a fusion with the Amyloid Precursor Protein (APP) or Human Growth Hormone (HGH) secretion signal. These unique expression systems allow for the production of high levels of HCV proteins, contributing to the proper processing, glycosylation and folding of the viral protein(s) in the system. In particular, the present invention provides the 15 plasmids pHCV-162, pHCV-167, pHCV-168, pHCV-169 and pHCV-170. The APP-HCV-E2 fusion proteins expressed by mammalian expression vectors pHCV-162 and pHCV-167 also are included. Further, HGH-HCV-E2 fusion proteins expressed by a mammalian expression vectors pHCV-168, pHCV-169 and pHCV-170 are provided.

20 The present invention also provides a method for detecting HCV antigen or antibody in a test sample suspected of containing HCV antigen or antibody, wherein the improvement comprises contacting the test sample with a glycosylated HCV antigen produced in a mammalian expression system. Also provided is a method for detecting HCV antigen or antibody in a test sample suspected of containing HCV antigen 25 or antibody, wherein the improvement comprises contacting the test sample with an antibody produced by using a glycosylated HCV antigen produced in a mammalian expression system. The antibody can be monoclonal or polyclonal.

The present invention further provides a test kit for detecting the presence of HCV antigen or HCV antigen in a test sample suspected of containing said HCV 30 antigen or antibody, comprising a container containing a glycosylated HCV antigen produced in a mammalian expression system. The test kit also can include an antibody produced by using a glycosylated HCV antigen produced in a mammalian expression system. Another test kit provided by the present invention comprises a container containing an antibody produced by using a glycosylated HCV antigen 35 produced in a mammalian expression system. The antibody provided by the test kits can be monoclonal or polyclonal.

Brief Description of the Drawings

Figure 1 presents a schematic representation of the strategy employed to generate and assemble HCV genomic clones.

5 Figure 2 presents a schematic representation of the location and amino acid composition of the APP-HCV-E2 fusion proteins expressed by the mammalian expression vectors pHCV-162 and pHCV-167.

Figure 3 presents a schematic representation of the mammalian expression vector pRC/CMV.

10 Figure 4 presents the RIPA results obtained for the APP-HCV-E2 fusion protein expressed by pHCV-162 in HEK-293 cells using HCV antibody positive human sera.

Figure 5 presents the RIPA results obtained for the APP-HCV-E2 fusion protein expressed by pHCV-162 in HEK-293 cells using rabbit polyclonal sera directed against synthetic peptides.

15 Figure 6 presents the RIPA results obtained for the APP-HCV-E2 fusion protein expressed by pHCV-167 in HEK-293 cells using HCV antibody positive human sera.

20 Figure 7 presents the Endoglycosidase-H digestion of the immunoprecipitated APP-HCV-E2 fusion proteins expressed by pHCV-162 and pHCV-167 in HEK-293 cells.

Figure 8 presents the RIPA results obtained when American HCV antibody positive sera were screened against the APP-HCV-E2 fusion protein expressed by pHCV-162 in HEK-293 cells.

25 Figure 9 presents the RIPA results obtained when the sera from Japanese volunteer blood donors were screened against the APP-HCV-E2 fusion protein expressed by pHCV-162 in HEK-293 cells.

Figure 10 presents the RIPA results obtained when the sera from Japanese volunteer blood donors were screened against the APP-HCV-E2 fusion protein expressed by pHCV-162 in HEK-293 cells.

30 Figure 11 presents a schematic representation of the mammalian expression vector pCDNA-I.

Figure 12 presents a schematic representation of the location and amino acid composition of the HGH-HCV-E1 fusion protein expressed by the mammalian expression vector pHCV-168.

35 Figure 13 presents a schematic representation of the location and amino acid composition of the HGH-HCV-E2 fusion proteins expressed by the mammalian expression vectors pHCV-169 and pHCV-170.

Figure 14 presents the RIPA results obtained when HCV E2 antibody positive sera were screened against the HGH-HCV-E1 fusion protein expressed by pHCV-168 in HEK-293 cells.

Figure 15 presents the RIPA results obtained when HCV E2 antibody positive sera were screened against the HGH-HCV-E2 fusion proteins expressed by pHCV-169 and pHCV-170 in HEK-293 cells.

Detailed Description of the Invention

The present invention provides full-length genomic clones useful in a variety of aspects. Such full-length genomic clones can allow culture of the HCV virus which in turn is useful for a variety of purposes. Successful culture of the HCV virus can allow for the development of viral replication inhibitors, viral proteins for diagnostic applications, viral proteins for therapeutics, and specifically structural viral antigens, including, for example, HCV putative envelope, HCV putative E1 and HCV putative E2 fragments.

Cell lines which can be used for viral replication are numerous, and include (but are not limited to), for example, primary hepatocytes, permanent or semi-permanent hepatocytes, cultures transfected with transforming viruses or transforming genes. Especially useful cell lines could include, for example, permanent hepatocyte cultures that continuously express any of several heterologous RNA polymerase genes to amplify HCV RNA sequences under the control of these specific RNA polymerase sequences.

Sources of HCV viral sequences encoding structural antigens include putative core, putative E1 and putative E2 fragments. Expression can be performed in both prokaryotic and eukaryotic systems. The expression of HCV proteins in mammalian expression systems allows for glycosylated proteins such as the E1 and E2 proteins, to be produced. These glycosylated proteins have diagnostic utility in a variety of aspects, including, for example, assay systems for screening and prognostic applications. The mammalian expression of HCV viral proteins allows for inhibitor studies including elucidation of specific viral attachment sites or sequences and/or viral receptors on susceptible cell types, for example, liver cells and the like.

The procurement of specific expression clones developed as described herein in mammalian expression systems provides antigens for diagnostic assays which can determine the stage of HCV infection, such as, for example, acute versus on-going or persistent infections, and/or recent infection versus past exposure. These specific expression clones also provide prognostic markers for resolution of disease such as to distinguish resolution of disease from chronic hepatitis caused by HCV. It is

contemplated that earlier seroconversion to glycosylated structural antigens possibly may be detected by using proteins produced in these mammalian expression systems. Antibodies, both monoclonal and polyclonal, also may be produced from the proteins derived from these mammalian expression systems which then in turn may 5 be used for diagnostic, prognostic and therapeutic applications. Also, reagents produced from these novel expression systems described herein may be useful in the characterization and or isolation of other infectious agents.

Proteins produced from these mammalian expression systems, as well as reagents produced from these proteins, can be placed into appropriate container and 10 packaged as test kits for convenience in performing assays. Other aspects of the present invention include a polypeptide comprising an HCV epitope attached to a solid phase and an antibody to an HCV epitope attached to a solid phase. Also included are methods for producing a polypeptide containing an HCV epitope comprising incubating host cells transformed with a mammalian expression vector containing a 15 sequence encoding a polypeptide containing an HCV epitope under conditions which allow expression of the polypeptide, and a polypeptide containing an HCV epitope produced by this method.

The present invention provides assays which utilize the recombinant or synthetic polypeptides provided by the invention, as well as the antibodies described 20 herein in various formats, any of which may employ a signal generating compound in the assay. Assays which do not utilize signal generating compounds to provide a means of detection also are provided. All of the assays described generally detect either antigen or antibody, or both, and include contacting a test sample with at least one reagent provided herein to form at least one antigen/antibody complex and 25 detecting the presence of the complex. These assays are described in detail herein.

Vaccines for treatment of HCV infection comprising an immunogenic peptide obtained from a mammalian expression system containing an HCV epitope, or an inactivated preparation of HCV, or an attenuated preparation of HCV also are included in the present invention. Also included in the present invention is a method 30 for producing antibodies to HCV comprising administering to an individual an isolated immunogenic polypeptide containing an HCV epitope in an amount sufficient to produce an immune response in the inoculated individual.

Also provided by the present invention is a tissue culture grown cell infected with HCV.

35 The term "antibody containing body component" (or test sample) refers to a component of an individual's body which is the source of the antibodies of interest. These components are well known in the art. These samples include biological

samples which can be tested by the methods of the present invention described herein and include human and animal body fluids such as whole blood, serum, plasma, cerebrospinal fluid, urine, lymph fluids, and various external sections of the respiratory, intestinal and genitourinary tracts, tears, saliva, milk, white blood cells, myelomas and the like, biological fluids such as cell culture supernatants, fixed tissue specimens and fixed cell specimens.

After preparing recombinant proteins, as described by the present invention, the recombinant proteins can be used to develop unique assays as described herein to detect either the presence of antigen or antibody to HCV. These compositions also can be used to develop monoclonal and/or polyclonal antibodies with a specific recombinant protein which specifically binds to the immunological epitope of HCV which is desired by the routineer. Also, it is contemplated that at least one recombinant protein of the invention can be used to develop vaccines by following methods known in the art.

It is contemplated that the reagent employed for the assay can be provided in the form of a kit with one or more containers such as vials or bottles, with each container containing a separate reagent such as a monoclonal antibody, or a cocktail of monoclonal antibodies, or a polypeptide (either recombinant or synthetic) employed in the assay.

"Solid phases" ("solid supports") are known to those in the art and include the walls of wells of a reaction tray, test tubes, polystyrene beads, magnetic beads, nitrocellulose strips, membranes, microparticles such as latex particles, and others. The "solid phase" is not critical and can be selected by one skilled in the art. Thus, latex particles, microparticles, magnetic or non-magnetic beads, membranes, plastic tubes, walls of microtiter wells, glass or silicon chips and sheep red blood cells are all suitable examples. Suitable methods for immobilizing peptides on solid phases include ionic, hydrophobic, covalent interactions and the like. A "solid phase", as used herein, refers to any material which is insoluble, or can be made insoluble by a subsequent reaction. The solid phase can be chosen for its intrinsic ability to attract and immobilize the capture reagent. Alternatively, the solid phase can retain an additional receptor which has the ability to attract and immobilize the capture reagent. The additional receptor can include a charged substance that is oppositely charged with respect to the capture reagent itself or to a charged substance conjugated to the capture reagent. As yet another alternative, the receptor molecule can be any specific binding member which is immobilized upon (attached to) the solid phase and which has the ability to immobilize the capture reagent through a specific binding reaction. The receptor molecule enables

the indirect binding of the capture reagent to a solid phase material before the performance of the assay or during the performance of the assay. The solid phase thus can be a plastic, derivatized plastic, magnetic or non-magnetic metal, glass or silicon surface of a test tube, microtiter well, sheet, bead, microparticle, chip, and 5 other configurations known to those of ordinary skill in the art.

It is contemplated and within the scope of the invention that the solid phase also can comprise any suitable porous material with sufficient porosity to allow access by detection antibodies and a suitable surface affinity to bind antigens.

10 Microporous structures are generally preferred, but materials with gel structure in the hydrated state may be used as well. Such useful solid supports include:

natural polymeric carbohydrates and their synthetically modified, cross-linked or substituted derivatives, such as agar, agarose, cross-linked alginic acid, substituted and cross-linked guar gums, cellulose esters, especially with nitric acid and carboxylic acids, mixed cellulose esters, and cellulose ethers; natural 15 polymers containing nitrogen, such as proteins and derivatives, including cross-linked or modified gelatins; natural hydrocarbon polymers, such as latex and rubber; synthetic polymers which may be prepared with suitably porous structures, such as vinyl polymers, including polyethylene, polypropylene, polystyrene, polyvinylchloride, polyvinylacetate and its partially hydrolyzed 20 derivatives, polyacrylamides, polymethacrylates, copolymers and terpolymers of the above polycondensates, such as polyesters, polyamides, and other polymers, such as polyurethanes or polyepoxides; porous inorganic materials such as sulfates or carbonates of alkaline earth metals and magnesium, including barium sulfate, calcium sulfate, calcium carbonate, silicates of alkali and alkaline earth metals, 25 aluminum and magnesium; and aluminum or silicon oxides or hydrides, such as clays, alumina, talc, kaolin, zeolite, silica gel, or glass (these materials may be used as filters with the above polymeric materials); and mixtures or copolymers of the above classes, such as graft copolymers obtained by initializing polymerization of synthetic polymers on a pre-existing natural polymer. All of these materials 30 may be used in suitable shapes, such as films, sheets, or plates, or they may be coated onto or bonded or laminated to appropriate inert carriers, such as paper, glass, plastic films, or fabrics.

The porous structure of nitrocellulose has excellent absorption and adsorption qualities for a wide variety of reagents including monoclonal antibodies. 35 Nylon also possesses similar characteristics and also is suitable. It is contemplated that such porous solid supports described hereinabove are preferably in the form of sheets of thickness from about 0.01 to 0.5 mm, preferably about 0.1 mm. The pore

size may vary within wide limits, and is preferably from about 0.025 to 15 microns, especially from about 0.15 to 15 microns. The surfaces of such supports may be activated by chemical processes which cause covalent linkage of the antigen or antibody to the support. The irreversible binding of the antigen or antibody is obtained, however, in general, by adsorption on the porous material by poorly understood hydrophobic forces. Suitable solid supports also are described in U.S. Patent Application Serial No. 227,272.

The "indicator reagent" comprises a "signal generating compound" (label) which is capable of generating a measurable signal detectable by external means conjugated (attached) to a specific binding member for HCV. "Specific binding member" as used herein means a member of a specific binding pair. That is, two different molecules where one of the molecules through chemical or physical means specifically binds to the second molecule. In addition to being an antibody member of a specific binding pair for HCV, the indicator reagent also can be a member of any specific binding pair, including either hapten-anti-hapten systems such as biotin or anti-biotin, avidin or biotin, a carbohydrate or a lectin, a complementary nucleotide sequence, an effector or a receptor molecule, an enzyme cofactor and an enzyme, an enzyme inhibitor or an enzyme, and the like. An immunoreactive specific binding member can be an antibody, an antigen, or an antibody/antigen complex that is capable of binding either to HCV as in a sandwich assay, to the capture reagent as in a competitive assay, or to the ancillary specific binding member as in an indirect assay.

The various "signal generating compounds" (labels) contemplated include chromogens, catalysts such as enzymes, luminescent compounds such as fluorescein and rhodamine, chemiluminescent compounds, radioactive elements, and direct visual labels. Examples of enzymes include alkaline phosphatase, horseradish peroxidase, beta-galactosidase, and the like. The selection of a particular label is not critical, but it will be capable of producing a signal either by itself or in conjunction with one or more additional substances.

The various "signal generating compounds" (labels) contemplated include chromogens, catalysts such as enzymes, luminescent compounds such as fluorescein and rhodamine, chemiluminescent compounds such as acridinium, phenanthridinium and dioxetane compounds, radioactive elements, and direct visual labels. Examples of enzymes include alkaline phosphatase, horseradish peroxidase, beta-galactosidase, and the like. The selection of a particular label is not critical, but it will be capable of producing a signal either by itself or in conjunction with one or more additional substances.

Other embodiments which utilize various other solid phases also are contemplated and are within the scope of this invention. For example, ion capture procedures for immobilizing an immobilizable reaction complex with a negatively charged polymer, described in co-pending U. S. Patent Application Serial No.

5 150,278 corresponding to EP publication 0326100, and U. S. Patent Application Serial No. 375,029 (EP publication no. 0406473) both of which enjoy common ownership and are incorporated herein by reference, can be employed according to the present invention to effect a fast solution-phase immunochemical reaction. An immobilizable immune complex is separated from the rest of the reaction mixture

10 by ionic interactions between the negatively charged poly-anion/immune complex and the previously treated, positively charged porous matrix and detected by using various signal generating systems previously described, including those described in chemiluminescent signal measurements as described in co-pending U.S. Patent Application Serial No.921,979 corresponding to EPO Publication No. 0 273,115,

15 which enjoys common ownership and which is incorporated herein by reference.

Also, the methods of the present invention can be adapted for use in systems which utilize microparticle technology including in automated and semi-automated systems wherein the solid phase comprises a microparticle. Such systems include those described in pending U. S. Patent Applications 425,651 and 425,643, which

20 correspond to published EPO applications Nos. EP 0 425 633 and EP 0 424 634, respectively, which are incorporated herein by reference.

The use of scanning probe microscopy (SPM) for immunoassays also is a technology to which the monoclonal antibodies of the present invention are easily adaptable. In scanning probe microscopy, in particular in atomic force microscopy,

25 the capture phase, for example, at-least one of the monoclonal antibodies of the invention, is adhered to a solid phase and a scanning probe microscope is utilized to detect antigen/antibody complexes which may be present on the surface of the solid phase. The use of scanning tunnelling microscopy eliminates the need for labels which normally must be utilized in many immunoassay systems to detect

30 antigen/antibody complexes. Such a system is described in pending U. S. patent application Serial No. 662,147, which enjoys common ownership and is incorporated herein by reference.

The use of SPM to monitor specific binding reactions can occur in many ways. In one embodiment, one member of a specific binding partner (analyte specific substance which is the monoclonal antibody of the invention) is attached to a surface suitable for scanning. The attachment of the analyte specific substance may be by adsorption to a test piece which comprises a solid phase of a plastic or

metal surface, following methods known to those of ordinary skill in the art. Or, covalent attachment of a specific binding partner (analyte specific substance) to a test piece which test piece comprises a solid phase of derivatized plastic, metal, silicon, or glass may be utilized. Covalent attachment methods are known to those skilled in the art and include a variety of means to irreversibly link specific binding partners to the test piece. If the test piece is silicon or glass, the surface must be activated prior to attaching the specific binding partner. Activated silane compounds such as triethoxy amino propyl silane (available from Sigma Chemical Co., St. Louis, MO), triethoxy vinyl silane (Aldrich Chemical Co., Milwaukee, WI), and (3-mercaptopropyl)-trimethoxy silane (Sigma Chemical Co., St. Louis, MO) can be used to introduce reactive groups such as amino-, vinyl, and thiol, respectively. Such activated surfaces can be used to link the binding partner directly (in the cases of amino or thiol) or the activated surface can be further reacted with linkers such as glutaraldehyde, bis (succinimidyl) suberate, SPPD 9 succinimidyl 3-[2-pyridyldithio] propionate), SMCC (succinimidyl-4-[N-maleimidomethyl] cyclohexane-1-carboxylate), SIAB (succinimidyl [4-iodoacetyl] aminobenzoate), and SMPB (succinimidyl 4-[1-maleimidophenyl] butyrate) to separate the binding partner from the surface. The vinyl group can be oxidized to provide a means for covalent attachment. It also can be used as an anchor for the polymerization of various polymers such as poly acrylic acid, which can provide multiple attachment points for specific binding partners. The amino surface can be reacted with oxidized dextrans of various molecular weights to provide hydrophilic linkers of different size and capacity. Examples of oxidizable dextrans include Dextran T-40 (molecular weight 40,000 daltons), Dextran T-110 (molecular weight 110,000 daltons), Dextran T-500 (molecular weight 500,000 daltons), Dextran T-2M (molecular weight 2,000,000 daltons) (all of which are available from Pharmacia, LOCATION), or Ficoll (molecular weight 70,000 daltons (available from Sigma Chemical Co., St. Louis, MO). Also, polyelectrolyte interactions may be used to immobilize a specific binding partner on a surface of a test piece by using techniques and chemistries described by pending U. S. Patent applications Serial No. 150,278, filed January 29, 1988, and Serial No. 375,029, filed July 7, 1989, each of which enjoys common ownership and each of which is incorporated herein by reference. The preferred method of attachment is by covalent means. Following attachment of a specific binding member, the surface may be further treated with materials such as serum, proteins, or other blocking agents to minimize non-specific binding. The surface also may be scanned either at the site of manufacture or point of use to verify its suitability for assay

purposes. The scanning process is not anticipated to alter the specific binding properties of the test piece.

Various other assay formats may be used, including "sandwich" immunoassays and competitive probe assays. For example, the monoclonal 5 antibodies produced from the proteins of the present invention can be employed in various assay systems to determine the presence, if any, of HCV proteins in a test sample. Fragments of these monoclonal antibodies provided also may be used. For example, in a first assay format, a polyclonal or monoclonal anti-HCV antibody or fragment thereof, or a combination of these antibodies, which has been coated on a 10 solid phase, is contacted with a test sample which may contain HCV proteins, to form a mixture. This mixture is incubated for a time and under conditions sufficient to form antigen/antibody complexes. Then, an indicator reagent comprising a monoclonal or a polyclonal antibody or a fragment thereof, which specifically binds to the HCV fragment, or a combination of these antibodies, to which a signal 15 generating compound has been attached, is contacted with the antigen/antibody complexes to form a second mixture. This second mixture then is incubated for a time and under conditions sufficient to form antibody/antigen/antibody complexes. The presence of HCV antigen present in the test sample and captured on the solid phase, if any, is determined by detecting the measurable signal generated by the 20 signal generating compound. The amount of HCV antigen present in the test sample is proportional to the signal generated.

Alternatively, a polyclonal or monoclonal anti-HCV antibody or fragment thereof, or a combination of these antibodies which is bound to a solid support, the test sample and an indicator reagent comprising a monoclonal or polyclonal antibody 25 or fragments thereof, which specifically binds to HCV antigen, or a combination of these antibodies to which a signal generating compound is attached, are contacted to form a mixture. This mixture is incubated for a time and under conditions sufficient to form antibody/antigen/antibody complexes. The presence, if any, of HCV proteins present in the test sample and captured on the solid phase is 30 determined by detecting the measurable signal generated by the signal generating compound. The amount of HCV proteins present in the test sample is proportional to the signal generated.

In another alternate assay format, one or a combination of one or more monoclonal antibodies of the invention can be employed as a competitive probe for 35 the detection of antibodies to HCV protein. For example, HCV proteins, either alone or in combination, can be coated on a solid phase. A test sample suspected of containing antibody to HCV antigen then is incubated with an indicator reagent

comprising a signal generating compound and at least one monoclonal antibody of the invention for a time and under conditions sufficient to form antigen/antibody complexes of either the test sample and indicator reagent to the solid phase or the indicator reagent to the solid phase. The reduction in binding of the monoclonal antibody to the solid phase can be quantitatively measured. A measurable reduction in the signal compared to the signal generated from a confirmed negative NANB hepatitis test sample indicates the presence of anti-HCV antibody in the test sample.

5 In yet another detection method, each of the monoclonal antibodies of the present invention can be employed in the detection of HCV antigens in fixed tissue sections, as well as fixed cells by immunohistochemical analysis.

10 In addition, these monoclonal antibodies can be bound to matrices similar to CNBr-activated Sepharose and used for the affinity purification of specific HCV proteins from cell cultures, or biological tissues such as blood and liver.

15 The monoclonal antibodies of the invention can also be used for the generation of chimeric antibodies for therapeutic use, or other similar applications.

20 The monoclonal antibodies or fragments thereof can be provided individually to detect HCV antigens. Combinations of the monoclonal antibodies (and fragments thereof) provided herein also may be used together as components in a mixture or "cocktail" of at least one anti-HCV antibody of the invention with antibodies to other HCV regions, each having different binding specificities. Thus, this cocktail can include the monoclonal antibodies of the invention which are directed to HCV proteins and other monoclonal antibodies to other antigenic determinants of the HCV genome.

25 The polyclonal antibody or fragment thereof which can be used in the assay formats should specifically bind to a specific HCV region or other HCV proteins used in the assay. The polyclonal antibody used preferably is of mammalian origin; human, goat, rabbit or sheep anti-HCV polyclonal antibody can be used. Most preferably, the polyclonal antibody is rabbit polyclonal anti-HCV antibody. The polyclonal antibodies used in the assays can be used either alone or as a cocktail of polyclonal antibodies. Since the cocktails used in the assay formats are comprised of either monoclonal antibodies or polyclonal antibodies having different HCV specificity, they would be useful for diagnosis, evaluation and prognosis of HCV infection, as well as for studying HCV protein differentiation and specificity.

30 In another assay format, the presence of antibody and/or antigen to HCV can be detected in a simultaneous assay, as follows. A test sample is simultaneously contacted with a capture reagent of a first analyte, wherein said capture reagent

comprises a first binding member specific for a first analyte attached to a solid phase and a capture reagent for a second analyte, wherein said capture reagent comprises a first binding member for a second analyte attached to a second solid phase, to thereby form a mixture. This mixture is incubated for a time and under 5 conditions sufficient to form capture reagent/first analyte and capture reagent/second analyte complexes. These so-formed complexes then are contacted with an indicator reagent comprising a member of a binding pair specific for the first analyte labelled with a signal generating compound and an indicator reagent comprising a member of a binding pair specific for the second analyte labelled with 10 a signal generating compound to form a second mixture. This second mixture is incubated for a time and under conditions sufficient to form capture reagent/first analyte/indicator reagent complexes and capture reagent/second analyte/indicator reagent complexes. The presence of one or more analytes is determined by detecting 15 a signal generated in connection with the complexes formed on either or both solid phases as an indication of the presence of one or more analytes in the test sample. In this assay format, proteins derived from human expression systems may be utilized as well as monoclonal antibodies produced from the proteins derived from the mammalian expression systems as disclosed herein. Such assay systems are described in greater detail in pending U.S. Patent Application Serial No. 20 07/574,821 entitled Simultaneous Assay for Detecting One Or More Analytes, filed August 29, 1990, which enjoys common ownership and is incorporated herein by reference.

In yet other assay formats, recombinant proteins may be utilized to detect the presence of anti-HCV in test samples. For example, a test sample is incubated 25 with a solid phase to which at least one recombinant protein has been attached. These are reacted for a time and under conditions sufficient to form antigen/antibody complexes. Following incubation, the antigen/antibody complex is detected. Indicator reagents may be used to facilitate detection, depending upon the assay system chosen. In another assay format, a test sample is contacted with a 30 solid phase to which a recombinant protein produced as described herein is attached and also is contacted with a monoclonal or polyclonal antibody specific for the protein, which preferably has been labelled with an indicator reagent. After incubation for a time and under conditions sufficient for antibody/antigen complexes to form, the solid phase is separated from the free phase, and the label is 35 detected in either the solid or free phase as an indication of the presence of HCV antibody. Other assay formats utilizing the proteins of the present invention are contemplated. These include contacting a test sample with a solid phase to which at

least one recombinant protein produced in the mammalian expression system has been attached, incubating the solid phase and test sample for a time and under conditions sufficient to form antigen/antibody complexes, and then contacting the solid phase with a labelled recombinant antigen. Assays such as this and others are 5 described in pending U.S. Patent Application Serial No. 07/787,710, which enjoys common ownership and is incorporated herein by reference.

While the present invention discloses the preference for the use of solid phases, it is contemplated that the proteins of the present invention can be utilized in non-solid phase assay systems. These assay systems are known to those skilled 10 in the art, and are considered to be within the scope of the present invention.

The present invention will now be described by way of examples, which are meant to illustrate, but not to limit, the spirit and scope of the invention.

EXAMPLES

15

Example 1: Generation of HCV Genomic Clones

RNA isolated from the serum or plasma of a chimpanzee (designated as "CO") experimentally infected with HCV, or an HCV seropositive human patient (designated as "LG") was transcribed to cDNA using reverse transcriptase employing either random hexamer primers or specific anti-sense primers derived. 20 from the prototype HCV-1 sequence. The sequence has been reported by Choo et al. (Choo et al., Proc. Nat'l. Acad. Sci. USA 88:2451-2455 [1991], and is available through GenBank data base, Accession No. M62321). This cDNA then was amplified using PCR and AmpliTaq[®] DNA polymerase (available in the Gene Amp Kit[®] from Perkin Elmer Cetus, Norwalk, Connecticut 06859) employing either a second sense 25 primer located -approximately 1000-2000 nucleotides upstream of the specific antisense primer or a pair of sense and antisense primers flanking a 1000-2000 nucleotide fragment of HCV. After 25 to 35 cycles of amplification following standard procedures known in the art, an aliquot of this reaction mixture was subjected to nested PCR (or "PCR-2"), wherein a pair of sense and antisense 30 primers located internal to the original pair of PCR primers was employed to further amplify HCV gene segments in quantities sufficient for analysis and subcloning, utilizing endonuclease recognition sequences present in the second set of PCR primers. In this manner, seven adjacent HCV DNA fragments were generated which then could be assembled using the generic cloning strategy presented and 35 described in FIGURE 1. The location of the specific primers used in this manner are presented in Table 1 and are numbered according to the HCV-1 sequence reported by Choo et al (GenBank data base, Accession No. M62321). Prior to

assembly, the DNA sequence of each of the individual fragments was determined and translated into the genomic amino acid sequences presented in SEQUENCE ID. NO. 1 and 2, respectively, for CO and LG, respectively. Comparison of the genomic polypeptide of CO with that of HCV-1 demonstrated 98 amino acid differences.

5 Comparison of the genomic polypeptide of CO with that of LG, demonstrated 150 amino acid differences. Comparison of the genomic polypeptide of LG with that of HCV-1 demonstrated 134 amino acid differences.

Example 2. Expression of the HCV E2 Protein As A Fusion

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With The Amyloid Precursor Protein (APP)

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The HCV E2 protein from CO developed as described in Example 1 was expressed as a fusion with the Amyloid Precursor Protein (APP). APP has been described by Kang et al., Nature 325:733-736 (1987). Briefly, HCV amino acids 384-749 of the CO isolate were used to replace the majority of the APP coding sequence as demonstrated in FIGURE 2. A HindIII-StyI DNA fragment representing the amino-terminal 66 amino acids and a BgIII-XbaI fragment representing the carboxyl-terminal 105 amino acids of APP were ligated to a PCR derived HCV fragment from CO representing HCV amino acids 384-749 containing StyI and BgIII restriction sites on its 5' and 3' ends, respectively. This APP-HCV-E2 fusion gene cassette then was cloned into the commercially available mammalian expression vector pRC/CMV shown in FIGURE 3, (available from Invitrogen, San Diego, CA) at the unique HindIII and XbaI sites. After transformation into E. coli DH5a, a clone designated pHCV-162 was isolated, which placed the expression of the APP-HCV-E2 fusion gene cassette under control of the strong CMV promotor. The complete nucleotide sequence of the mammalian expression vector pHCV-162 is presented in SEQUENCE ID. NO. 3. Translation of nucleotides 922 through 2535 results in the complete amino acid sequence of the APP-HCV-E2 fusion protein expressed by pHCV-162 as presented in SEQUENCE ID. NO. 4.

20

A primary Human Embryonic Kidney (HEK) cell line transformed with human adenovirus type 5, designated as HEK-293, was used for all transfections and expression analyses. HEK-293 cells were maintained in Minimum Essential Medium (MEM) which was supplemented with 10% fetal calf serum (FCS), penicillin and streptomycin.

25

Approximately 20 µg of purified DNA from pHCV-162 was transfected into HEK-293 cells using the modified calcium phosphate protocol as reported by Chen et al., Molecular and Cellular Biology 7(8):2745-2752 (1987). The calcium-phosphate-DNA solution was incubated on the HEK-293 cells for about 15 to 24

hours. The solution was removed, the cells were washed twice with MEM media, and then the cells were incubated in MEM media for an additional 24 to 48 hours. In order to analyze protein expression, the transfected cells were metabolically labelled with 100 μ Ci/ml S-35 methionine and cysteine for 12 to 18 hours. The 5 culture media was removed and stored, and the cells were washed in MEM media and then lysed in phosphate buffered saline (PBS) containing 1% Triton X-100® (available from Sigma Chemical Co., St. Louis, MO), 0.1% sodium dodecyl sulfate (SDS), and 0.5% deoxycholate, designated as PBS-TDS. This cell lysate then was frozen at -70°C for 2 to 24 hours, thawed on ice and then clarified by 10 centrifugation at 50,000 x g force for one hour at 4°C. Standard radio-immunoprecipitation assays (RIPAs) then were conducted on those labelled cell lysates and/or culture medias. Briefly, labelled cell lysates and/or culture medias were incubated with 2 to 5 μ l of specific sera at 4°C for one hour. Protein-A sepharose then was added and the samples were further incubated for one hour at 15 4°C with agitation. The samples were then centrifuged and the pellets washed several times with PBS-TDS buffer. Proteins recovered by immunoprecipitation were eluted by heating in an electrophoresis sample buffer (50 mM Tris-HCl, pH 6.8, 100 mM dithiothreitol [DTT], 2% SDS, 0.1% bromophenol blue, and 10% glycerol) for five minutes at 95°C. The eluted proteins then were separated by SDS 20 polyacrylamide gels which were subsequently treated with a fluorographic reagent such as Enlightening® (available from NEN [DuPont], Boston, MA), dried under vacuum and exposed to x-ray film at -70°C with intensifying screens. FIGURE 4 presents a RIPA analysis of pHCV-162 transfected HEK cell lysate precipitated with normal human sera (NHS), a monoclonal antibody directed against APP sequences 25 which were replaced in this construct (MAB), and an HCV antibody positive human sera (#25). Also presented in FIGURE 4 is the culture media (supernatant) precipitated with the same HCV antibody positive human sera (#25). From FIGURE 4, it can be discerned that while only low levels of an HCV specific protein of approximately 75K daltons is detected in the culture media of HEK-293 cells 30 transfected with pHCV-162, high levels of intracellular protein expression of the APP-HCV-E2 fusion protein of approximately 70K daltons is evident.

In order to further characterize this APP-HCV-E2 fusion protein, rabbit polyclonal antibody raised against synthetic peptides were used in a similar RIPA, the results of which are illustrated in FIGURE 5. As can be discerned from this 35 Figure, normal rabbit serum (NRS) does not precipitate the 70K dalton protein while rabbit sera raised against HCV amino acids 509-551 (6512), HCV amino

acids 380-436 (6521), and APP amino acids 45-62 (anti- N-terminus) are highly specific for the 70K dalton APP-HCV-E2 fusion protein.

In order to enhance secretion of this APP-HCV-E2 fusion protein, another clone was generated which fused only the amino-terminal 66 amino acids of APP, which contain the putative secretion signal sequences to the HCV-E2 sequences. In addition, a strongly hydrophobic sequence at the carboxyl-terminal end of the HCV-E2 sequence which was identified as a potential transmembrane spanning region was deleted. The resulting clone was designated as pHCV-167 and is schematically illustrated in FIGURE 2. The complete nucleotide sequence of the mammalian expression vector pHCV-167 is presented in SEQUENCE ID. NO. 5. Translation of nucleotides 922 through 2025 results in the complete amino acid sequence of the APP-HCV-E2 fusion protein expressed by pHCV-167 as presented in SEQUENCE ID. NO. 6. Purified DNA of pHCV-167 was transfected into HEK-293 cells and analyzed by RIPA and polyacrylamide SDS gels as described previously herein. FIGURE 6 presents the results in which a normal human serum sample (NHS) failed to recognize the APP-HCV-E2 fusion protein present in either the cell lysate or the cell supernatant of HEK-293 cells transfected with pHCV-167. The positive control HCV serum sample (#25), however, precipitated an approximately 65K dalton APP-HCV-E2 fusion protein present in the cell lysate of HEK-293 cells transfected with pHCV-167. In addition, substantial quantities of secreted APP-HCV-E2 protein of approximately 70K daltons was precipitated from the culture media by serum #25.

Digestion with Endoglycosidase-H (Endo-H) was conducted to ascertain the extent and composition of N-linked glycosylation in the APP-HCV E2 fusion proteins expressed by pHCV-167 and pHCV-162 in HEK-293 cells. Briefly, multiple aliquots of labelled cell lysates from pHCV-162 and pHCV-167 transfected HEK-293 cells were precipitated with human serum #50 which contained antibody to HCV E2 as previously described. The Protein-A sepharose pellet containing the immunoprecipitated protein-antibody complex was then resuspended in buffer (75mM sodium acetate, 0.05% SDS) containing or not containing 0.05 units per ml of Endo-H (Sigma). Digestions were performed at 37°C for 12 to 18 hours and all samples were analyzed by polyacrylamide SDS gels as previously described. FIGURE 7 presents the results of Endo-H digestion. Carbon-14 labelled molecular weight standards (MW) (obtained from Amersham, Arlington Heights, IL) are common on all gels and represent 200K, 92.5K, 69K, 46K, 30K and 14.3K daltons, respectively. Normal human serum (NHS) does not immunoprecipitate the APP-HCV-E2 fusion protein expressed by either pHCV-162 or pHCV-167, while

human serum positive for HCV E2 antibody (#50) readily detects the 72K dalton APP-HCV-E2 fusion protein in pHCV-162 and the 65K dalton APP-HCV E2 fusion protein in pHCV-167. Incubation of these immunoprecipitated proteins in the absence of Endo-H (#50 -Endo-H) does not significantly affect the quantity or 5 mobility of either pHCV-162 or pHCV-167 expressed proteins. Incubation in the presence of Endo-H (#50 +Endo-H), however, drastically reduces the mobility of the proteins expressed by pHCV-162 and pHCV-167, producing a heterogenous size distribution. The predicted molecular weight of the non-glycosylated polypeptide backbone of pHCV-162 is approximately 59K daltons. Endo-H treatment of pHCV- 10 162 lowers the mobility to a minimum of approximately 44K daltons, indicating that the APP-HCV-E2 fusion protein produced by pHCV-162 is proteolytically cleaved at the carboxyl-terminal end. A size of approximately 44K daltons is consistent with cleavage at or near HCV amino acid 720. Similarly, Endo-H treatment of pHCV-167 lowers the mobility to a minimum of approximately 41K 15 daltons, which compares favorably with the predicted molecular weight of approximately 40K daltons for the intact APP-HCV-E2 fusion protein expressed by pHCV-167.

Example 3 Detection of HCV E2 Antibodies

20 Radio-immunoprecipitation assay (RIPA) and polyacrylamide SDS gel analysis previously described was used to screen numerous serum samples for the presence of antibody directed against HCV E2 epitopes. HEK-293 cells transfected with pHCV-162 were metabolically labelled and cell lysates prepared as previously described. In addition to RIPA analysis, all serum samples were screened for the 25 presence of antibodies directed against specific HCV recombinant antigens representing distinct areas of the HCV genome using the Abbott Matrix® System. (available from Abbott Laboratories, Abbott Park, IL 60064, U.S. No. Patent 5,075,077). In the Matrix data presented in Tables 2 through 7, C100 yeast represents the NS4 region containing HCV amino acids 1569-1930, C100 E.coli 30 represents HCV amino acids 1676-1930, NS3 represents HCV amino acids 1192-1457, and CORE represents HCV amino acids 1-150.

FIGURE 8 presents a representative RIPA result obtained using pHCV-162 cell lysate to screen HCV antibody positive American blood donors and transfusion recipients. Table 2 summarizes the antibody profile of these various American 35 blood samples, with seven of seventeen (41%) samples demonstrating HCV E2 antibody. Genomic variability in the E2 region has been demonstrated between different HCV isolates, particularly in geographically distinct isolates which may

lead to differences in antibody responses. We therefore screened twenty-six Japanese volunteer blood donors and twenty Spanish hemodialysis patients previously shown to contain HCV antibody for the presence of specific antibody to the APP-HCV E2 fusion protein expressed by pHCV-162. Figures 9 and 10 present 5 the RIPA analysis on twenty-six Japanese volunteer blood donors. Positive control human sera (#50) and molecular weight standards (MW) appear in both figures in which the specific immunoprecipitation of the approximately 72K dalton APP-HCV-E2 fusion protein is demonstrated for several of the serum samples tested. Table 3 presents both the APP-HCV-E2 RIPA and Abbott Matrix® results 10 summarizing the antibody profiles of each of the twenty-six Japanese samples tested. Table 4 presents similar data for the twenty Spanish hemodialysis patients tested. Table 5 summarizes the RIPA results obtained using pHCV-162 to detect HCV E2 specific antibody in these various samples. Eighteen of twenty-six (69%) Japanese volunteers blood donors, fourteen of twenty (70%) Spanish hemodialysis 15 patients, and seven of seventeen (41%) American blood donors or transfusion recipients demonstrated a specific antibody response against the HCV E2 fusion protein. The broad immunoreactivity demonstrated by the APP-HCV-E2 fusion protein expressed by pHCV-162 suggests the recognition of conserved epitopes within HCV E2.

20 Serial bleeds from five transfusion recipients which seroconverted to HCV antibody were also screened using the APP-HCV-E2 fusion protein expressed by pHCV-162. This analysis was conducted to ascertain the time interval after exposure to HCV at which E2 specific antibodies can be detected. Table 6 presents one such patient (AN) who seroconverted to NS3 at 154 days post transfusion 25 (DPT). Antibodies to HCV E2 were not detected by RIPA until 271 DPT. Table 7 presents another such patient (WA), who seroconverted to CORE somewhere before 76 DPT and was positive for HCV E2 antibodies on the next available bleed date (103 DPT). Table 8 summarizes the serological results obtained from these five transfusion recipients indicating (a) some general antibody profile at 30 seroconversion (AB Status); (b) the days post transfusion at which an ELISA test would most likely detect HCV antibody (2.0 GEN); (c) the samples in which HCV E2 antibody was detected by RIPA (E2 AB Status); and (d) the time interval covered by the bleed dates tested (Samples Tested). The results indicate that antibody to HCV E2, as detected in the RIPA procedure described here, appears after seroconversion 35 to at least one other HCV marker (CORE, NS3, C100, etc.) and is persistent in nature once it appears. In addition, the absence of antibody to the structural gene CORE appears highly correlated with the absence of detectable antibody to E2.

another putative structural antigen. Further work is ongoing to correlate the presence or absence of HCV gene specific antibodies with progression of disease and/or time interval since exposure to HCV viral antigens.

5

Example 4 Expression of HCV E1 and E2 Using
Human Growth Hormone Secretion Signal

HCV DNA fragments representing HCV E1 (HCV amino acids 192 to 384) and HCV E2 (HCV amino acids 384-750 and 384-684) were generated from the CO isolate using PCR as described in Example 2. An Eco RI restriction site was used to 10 attach a synthetic oligonucleotide encoding the Human Growth Hormone (HGH) secretion signal (Blak et al, Oncogene, 3 129-136, 1988) at the 5' end of these HCV sequence. The resulting fragment was then cloned into the commercially available mammalian expression vector pCDNA-I, (available from Invitrogen, San Diego, California) illustrated in FIGURE 11. Upon transformation into E. coli 15 MC1061/P3, the resulting clones place the expression of the cloned sequence under control of the strong CMV promoter. Following the above outlined methods, a clone capable of expressing HCV-E1 (HCV amino acids 192-384) employing the HGH secretion signal at the extreme amino-terminal end was isolated. The clone was designated pHCV-168 and is schematically illustrated in FIGURE 12. Similarly, 20 clones capable of expressing HCV E2 (HCV amino acids 384-750 or 384-684) employing the HGH secretion signal were isolated, designated pHCV-169 and pHCV-170 respectively and illustrated in FIGURE 13. The complete nucleotide sequence of the mammalian expression vectors pHCV-168, pHCV-169, and pHCV-170 are presented in Sequence ID. NO. 7, 9, and 11 respectively. Translation of 25 nucleotides 2227 through 2913 results in the complete amino acid sequence of the HGH-HCV-E1 fusion protein expressed by pHCV-168 as presented in Sequence ID. NO. 8. Translation of nucleotides 2227 through 3426 results in the complete amino acid sequence of the HGH-HCV-E2 fusion protein expressed by pHCV-169 as presented in Sequence ID. NO. 10. Translation of nucleotides 2227 through 3228 30 results in the complete amino acid sequence of the HGH-HCV-E2 fusion protein expressed by pHCV-170 as presented in Sequence ID. NO. 12. Purified DNA from pHCV-168, pHCV-169, and pHCV-170 was transfected into HEK-293 cells which were then metabolically labelled, cell lysates prepared, and RIPA analysis performed as described previously herein. Seven sera samples previously shown to 35 contain antibodies to the APP-HCV-E2 fusion protein expressed by pHCV-162 were screened against the labelled cell lysates of pHCV-168, pHCV-169, and pHCV-170. Figure 14 presents the RIPA analysis for pHCV-168 and demonstrated that five

sera containing HCV E2 antibodies also contain HCV E1 antibodies directed against an approximately 33K dalton HGH-HCV-E1 fusion protein (#25, #50, 121, 503, and 728), while two other sera do not contain those antibodies (476 and 505). Figure 15 presents the RIPA results obtained when the same sera indicated above 5 were screened against the labelled cell lysates of either pHCV-169 or pHCV-170. All seven HCV E1 antibody positive sera detected two protein species of approximately 70K and 75K daltons in cells transfected with pHCV-168. These two different HGH-HCV-E2 protein species could result from incomplete proteolytic cleavage of the HCV E2 sequence at the carboxyl-terminal end (at or near HCV amino 10 acid 720) or from differences in carbohydrate processing between the two species. All seven HCV E2 antibody positive sera detected a single protein species of approximately 62K daltons for the HGH-HCV-E2 fusion protein expressed by pHCV-170. Table 9 summarizes the serological profile of six of the seven HCV E2 antibody positive sera screened against the HGH-HCV-E1 fusion protein expressed 15 by pHCV-170. Further work is ongoing to correlate the presence or absence of HCV gene specific antibodies with progression of disease and/or time interval since exposure to HCV viral antigens.

Clones pHCV-167 and pHCV-162 have been deposited at the American Type 20 Culture Collection, 12301 Parklawn Drive, Rockville, Maryland, 20852, as of January 17, 1992 under the terms of the Budapest Treaty, and accorded the following ATCC Designation Numbers: Clone pHCV-167 was accorded ATCC deposit number 68893 and clone pHCV-162 was accorded ATCC deposit number 68894. Clones pHCV-168, pHCV-169 and pHCV-170 have been deposited at the American 25 Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland, 20852, as of January 26, 1993 under the terms of the Budapest Treaty, and accorded the following ATCC Designation Numbers: Clone pHCV-168 was accorded ATCC deposit number 69228, clone pHCV-169 was accorded ATCC deposit number 69229 and clone pHCV-170 was accorded ATCC deposit number 69230. The designated deposits 30 will be maintained for a period of thirty (30) years from the date of deposit, or for five (5) years after the last request for the deposit; or for the enforceable life of the U.S. patent, whichever is longer. These deposits and other deposited materials mentioned herein are intended for convenience only, and are not required to practice the invention in view of the descriptions herein. The HCV cDNA sequences in all of 35 the deposited materials are incorporated herein by reference.

Other variations of applications of the use of the proteins and mammalian expression systems provided herein will be apparent to those skilled in the art.

Accordingly, the invention is intended to be limited only in accordance with the appended claims.

TABLE 1

5

FRAGMENT	PCR-1 PRIMERS		PCR-2 PRIMERS	
	SENSE	ANTISENSE	SENSE	ANTISENSE
1	1-17	1376-1400	14-31	1344-1364
2	1320-1344	2332-2357	1357-1377	2309-2327
3	2288-2312	3245-3269	2322-2337	3224-3242
4	3178-3195	5303-5321	3232-3252	5266-5289
5	5229-5249	6977-6996	5273-5292	6940-6962
6	6907-6925	8221-8240	6934-6954	8193-8216
7	8175-8194	9385-9401	8199-8225	9363-9387

10

TABLE 2
AMERICAN HCV POSITIVE SERA

SAMPLE	C100 YEAST S/CO	C100 ECOLT S/CO	NS3 S/CO	CORE S/CO	E2 RIPA
22	0.31	1.09	1.72	284.36	+
32	0.02	0.10	7.95	331.67	-
35	0.43	0.68	54.61	2.81	-
37	136.24	144.29	104.13	245.38	+
50	101.04	133.69	163.65	263.72	+
108	39.07	34.55	108.79	260.47	-
121	1.28	4.77	172.65	291.82	+
128	0.06	0.06	0.87	298.49	-
129	0.00	0.02	107.11	0.00	-
142	8.45	8.88	73.93	2.32	-
156	0.45	0.14	0.67	161.84	-
163	1.99	3.26	11.32	24.36	-
MI	89.9	118.1	242.6	120.4	-
KE	167.2	250.9	0.8	0.3	-
WA	164.4	203.3	223.9	160.9	+
PA	50.6	78.8	103.8	78.0	+
AN	224.8	287.8	509.9	198.8	+

TABLE 3
JAPANESE HCV POSITIVE BLOOD DONORS

5 SAMPLE	C100 YEAST S/CO	C100 ECOLT S/CO	NS3 S/CO	OCPE S/CO	E2 RIPA
410	86.33	93.59	9.68	257.82	+
435	0.18	0.18	0.69	39.25	+
441	0.20	0.09	0.17	6.51	-
476	0.37	1.29	144.66	302.35	+
496	39.06	37.95	2.78	319.99	-
560	1.08	0.68	3.28	26.59	-
589	0.06	1.28	117.82	224.23	+
620	0.17	1.37	163.41	256.64	+
622	123.46	162.54	154.67	243.44	+
623	23.46	26.55	143.72	277.24	+
633	0.01	0.43	161.84	264.02	+
639	1.40	2.23	12.15	289.80	+
641	0.01	0.08	8.65	275.00	+
648	-0.00	0.03	0.79	282.64	+
649	97.00	127.36	147.46	194.73	+
657	4.12	6.33	141.04	256.57	+
666	0.14	0.24	5.90	60.82	-
673	72.64	90.11	45.31	317.66	+
677	0.05	0.23	2.55	99.67	-
694	86.72	87.18	45.43	248.80	+
696	0.02	-0.02	0.26	12.55	-
706	17.02	12.96	153.77	266.87	+
717	0.04	0.02	0.15	10.46	-
728	-0.01	0.26	90.37	246.30	+
740	0.02	0.10	0.25	46.27	-
743	1.95	1.56	133.23	254.25	+

TABLE 4
SPANISH HEMODIALYSIS PATIENTS

SAMPLE	C100 YEAST S/CO	C100 ECOLI S/CO	NS3 S/CO	CORE S/CO	E2 RIPA
1	0.0	0.3	188.6	-0.0	-
2	129.3	142.8	165.4	201.0	+
3	113.7	128.5	154.5	283.3	+
5	130.6	143.8	133.4	186.1	+
6	56.2	63.4	93.6	32.0	+
7	0.0	0.2	72.1	211.5	+
8	156.7	171.9	155.1	227.0	+
9	65.3	78.9	76.1	102.6	+
10	136.7	149.3	129.4	190.2	+
11	0.0	0.7	155.7	272.4	+
12	1.0	1.9	143.6	210.6	+
13	0.0	0.3	111.2	91.1	-
14	1.1	3.1	94.7	214.8	-
15	45.9	66.1	106.3	168.2	+
16	36.3	68.8	149.3	0.1	-
17	121.0	129.9	113.4	227.8	+
18	64.8	99.7	138.9	0.2	-
19	25.6	34.1	157.4	254.9	+
20	104.9	125.1	126.8	218.3	+
21	48.1	68.5	0.8	49.4	-

TABLE 5
ANTIBODY RESPONSE TO HCV PROTEINS

	C100 YEAST S/CO	C100 E. COLI S/CO	NS3 S/CO	CORE S/CO	E2 RIPA
AMERICAN BLOOD DONORS	11/17	12/17	14/17	15/17	7/17
SPANISH HEMODIALYSIS PATIENTS	16/20	16/20	19/20	17/20	14/20
JAPANESE BLOOD DONORS	12/26	14/26	20/26	26/26	18/26

TABLE 6
HUMAN TRANSFUSION RECIPIENT (AN)

5

DAYs POST TRANS	C100 YEAST S/CO	C100 E. COLI S/CO	NS3 S/CO	CORE S/CO	E2 RIPA
29	1.8	1.9	8.9	1.1	-
57	0.4	0.3	1.2	0.4	-
88	0.3	0.3	0.4	0.7	-
116	0.1	0.2	0.5	0.2	-
154	0.3	0.7	65.3	0.8	-
179	18.0	21.5	445.6	1.5	-
271	257.4	347.2	538.0	3.1	+
376	240.0	382.5	513.5	139.2	+
742	292.9	283.7	505.3	198.1	+
1105	282.1	353.9	456.1	202.2	+
1489	224.8	287.8	509.9	198.8	+

10

TABLE 7
HUMAN TRANSFUSION RECIPIENT (WA)

DAYs POST TRANS	C100 YEAST S/CO	C100 E. COLI S/CO	NS3 S/CO	CORE S/CO	E2 RIPA
43	0.1	0.6	0.4	1.2	-
76	0.1	0.1	0.9	72.7	-
103	0.0	0.6	1.4	184.4	+
118	3.7	3.7	1.9	208.7	+
145	83.8	98.9	12.3	178.0	+
158	142.1	173.8	134.3	185.2	+
174	164.4	203.3	223.9	160.9	+

15

TABLE 8
HUMAN TRANSFUSION RECIPIENTS

	<u>AB STATUS</u>	<u>2.0 GEN</u>	<u>E2AB STATUS</u>	<u>SAMPLES TESTED</u>
MI	STRONG RESPONSE	78 DPT	NEG.	1-178 DPT
KE	EARLY C100	103 DPT	NEG.	1-166 DPT
WA	EARLY CORE	76 DPT	POS. 103-173 DPT	1-173 DPT
PA	EARLY C100	127 DPT	POS. 1491-3644 DPT	1-3644 DPT
AN	EARLY 33C	179 DPT	POS. 271-1489 DPT	1-1489 DPT

5

TABLE 9
SELECTED HCV E2 ANTIBODY POSITIVE SAMPLES

10	<u>SAMPLE</u>	<u>C100 YEAST S/CO</u>	<u>C100 E.COLI S/CO</u>	<u>NS3 S/CO</u>	<u>CORE S/CO</u>	<u>E2 RIPA</u>
	50	101.04	133.69	163.65	263.72	+
	121	1.28	4.77	172.65	291.82	+
	503	113.7	128.5	154.5	283.3	+
	505	130.6	143.8	133.4	186.1	-
	476	0.37	1.29	144.66	302.35	-
	728	-0.01	0.26	90.37	246.30	+

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: CASEY, JAMES M.
BODE, SUZANNE L.
ZECK, BILLY J.
YAMAGUCHI, JULIE
FRAIL, DONALD E.
DESAI, SURESH M.
DEVARE, SUSHIL G.

(ii) TITLE OF INVENTION: MAMMALIAN EXPRESSION SYSTEMS FOR HCV
PROTEINS

(iii) NUMBER OF SEQUENCES: 12

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: ABBOTT LABORATORIES D377/AP6D
(B) STREET: ONE ABBOTT PARK ROAD
(C) CITY: ABBOTT PARK
(D) STATE: IL
(E) COUNTRY: USA
(F) ZIP: 60064-3500

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: POREMBSKI, PRISCILLA E.
(B) REGISTRATION NUMBER: 33,207
(C) REFERENCE/DOCKET NUMBER: 5131.PC.01

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 708-937-6365
(B) TELEFAX: 708-937-9556

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3011 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn
1 5 10 15

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gln Ile Val Gly
20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
35 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
50 55 60

Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly
65 70 75 80

Tyr Prc Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp
85 90 95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro
100 105 110

Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys
115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu
130 135 140

Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
145 150 155 160

Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
165 170 175

Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser Ala Tyr
180 185 190

Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val Thr Asn Asp Cys Pro
195 200 205

Asn Ser Ser Ile Val Tyr Glu Ala Ala Asp Ala Ile Leu His Thr Pro
210 215 220

Gly Cys Val Pro Cys Val Arg Glu Gly Asn Ala Ser Arg Cys Trp Val
225 230 235 240

Ala Val Thr Pro Thr Val Ala Thr Arg Asp Gly Lys Leu Pro Thr Thr
245 250 255

Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser Ala Thr Leu Cys

260	265	270
Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Phe Leu Val Gly		
275	280	285
Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr Gln Asp Cys		
290	295	300
Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg Met Ala Trp		
305	310	315
Asp Met Met Met Asn Trp Ser Pro Thr Ala Ala Leu Val Val Ala Gln		
325	330	335
Leu Leu Arg Ile Pro Gln Ala Ile Leu Asp Met Ile Ala Gly Ala His		
340	345	350
Trp Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser Met Val Gly Asn Trp		
355	360	365
Ala Lys Val Leu Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu		
370	375	380
Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala Gly Leu Val		
385	390	395
Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu Ile Asn Thr		
405	410	415
Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys Asn Glu Ser		
420	425	430
Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe Asn		
435	440	445
Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg Leu Thr Asp		
450	455	460
Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly Ser Gly Leu		
465	470	475
Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Pro Cys Gly Ile		
485	490	495
Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro Ser		
500	505	510
Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr Tyr Ser		
515	520	525
Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg Pro		
530	535	540
Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly Phe		
545	550	555
560		

Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly Val Gly Asn
 565 570 575
 Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys His Pro Glu Ala
 580 585 590
 Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg Cys Met
 595 600 605
 Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile Asn Tyr
 610 615 620
 Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu His Arg Leu
 625 630 635 640
 Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu Glu Asp
 645 650 655
 Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Ser Thr Thr Gln Trp
 660 665 670
 Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Ser Thr Gly
 675 680 685
 Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu Tyr Gly
 690 695 700
 Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu Tyr Val Val
 705 710 715 720
 Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys Ser Cys Leu Trp
 725 730 735
 Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu Asn Leu Val
 740 745 750
 Ile Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly Phe Val Ser Phe
 755 760 765
 Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly Arg Trp Val Pro
 770 775 780
 Gly Ala Ala Tyr Ala Leu Tyr Gly Ile Trp Pro Leu Leu Leu Leu
 785 790 795 800
 Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr Glu Val Ala Ala
 805 810 815
 Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala Leu Thr Leu Ser
 820 825 830
 Pro Tyr Tyr Lys Arg Tyr Ile Ser Trp Cys Met Trp Trp Leu Gln Tyr
 835 840 845

Phe Leu Thr Arg Val Glu Ala Gln Leu His Val Trp Val Pro Pro Leu
 850 855 860

 Asn Val Arg Gly Gly Arg Asp Ala Val Ile Leu Leu Met Cys Ala Val
 865 870 875 880

 His Pro Thr Leu Val Phe Asp Ile Thr Lys Leu Leu Leu Ala Ile Phe
 885 890 895

 Gly Pro Leu Trp Ile Leu Gln Ala Ser Leu Leu Lys Val Pro Tyr Phe
 900 905 910

 Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu Ala Arg Lys Ile
 915 920 925

 Ala Gly Gly His Tyr Val Gln Met Ile Phe Ile Lys Leu Gly Ala Leu
 930 935 940

 Thr Gly Thr Tyr Val Tyr Asn His Leu Thr Pro Leu Arg Asp Trp Ala
 945 950 955 960

 His Asn Gly Leu Arg Asp Leu Ala Val Ala Val Glu Pro Val Val Phe
 965 970 975

 Ser Arg Met Glu Thr Lys Leu Ile Thr Trp Gly Ala Asp Thr Ala Ala
 980 985 990

 Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala Arg Arg Gly Gln
 995 1000 1005

 Glu Ile Leu Leu Gly Pro Ala Asp Gly Met Val Ser Lys Gly Trp Arg
 1010 1015 1020

 Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr Arg Gly Leu Leu
 1025 1030 1035 1040

 Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu
 1045 1050 1055

 Gly Glu Val Gln Ile Val Ser Thr Ala Thr Gln Thr Phe Leu Ala Thr
 1060 1065 1070

 Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Thr Arg
 1075 1080 1085

 Thr Ile Ala Ser Pro Lys Gly Pro Val Ile Gln Met Tyr Thr Asn Val
 1090 1095 1100

 Asp Gln Asp Leu Val Gly Trp Pro Ala Pro Gln Gly Ser Arg Ser Leu
 1105 1110 1115 1120

 Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His
 1125 1130 1135

 Ala Asp Val Ile Pro Val Arg Arg Gln Gly Asp Ser Arg Gly Ser Leu

1140	1145	1150
Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro		
1155	1160	1165
Leu Leu Cys Pro Ala Gly His Ala Val Gly Leu Phe Arg Ala Ala Val		
1170	1175	1180
Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Ile Pro Val Glu Asn		
1185	1190	1195
Leu Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro		
1205	1210	1215
Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr		
1220	1225	1230
Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly		
1235	1240	1245
Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe		
1250	1255	1260
Gly Ala Tyr Met Ser Lys Ala His Gly Val Asp Pro Asn Ile Arg Thr		
1265	1270	1275
Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr		
1285	1290	1295
Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Ala Tyr Asp Ile		
1300	1305	1310
Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly		
1315	1320	1325
Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val		
1330	1335	1340
Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro		
1345	1350	1355
Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr		
1365	1370	1375
Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile		
1380	1385	1390
Phe Cys His Ser Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val		
1395	1400	1405
Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser		
1410	1415	1420
Val Ile Pro Ala Ser Gly Asp Val Val Val Ser Thr Asp Ala Leu		
1425	1430	1435
1440		

Met Thr Gly Phe Thr Gly Asp Phe Asp Pro Val Ile Asp Cys Asn Thr
1445 1450 1455

Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile
1460 1465 1470

Glu Thr Thr Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg
1475 1480 1485

Gly Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro
1490 1495 1500

Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys
1505 1510 1515 1520

Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr
1525 1530 1535

Val Arg Leu Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln
1540 1545 1550

Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile
1555 1560 1565

Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Phe Pro
1570 1575 1580

Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro
1585 1590 1595 1600

Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro
1605 1610 1615

Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln
1620 1625 1630

Asn Glu Ile Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys
1635 1640 1645

Met Ser Ala Asn Pro Glu Val Val Thr Ser Thr Trp Val Leu Val Gly
1650 1655 1660

Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val
1665 1670 1675 1680

Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro Ala Ile Ile Pro
1685 1690 1695

Asp Arg Glu Val Leu Tyr Gln Glu Phe Asp Glu Met Glu Glu Cys Ser
1700 1705 1710

Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe
1715 1720 1725

Lys Gln Glu Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu
 1730 1735 1740

 Val Ile Thr Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Ala Phe
 1745 1750 1755 1760

 Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Thr Gln Tyr Leu Ala
 1765 1770 1775

 Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala
 1780 1785 1790

 Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu
 1795 1800 1805

 Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly
 1810 1815 1820

 Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly
 1825 1830 1835 1840

 Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu Ala Gly Tyr Gly
 1845 1850 1855

 Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu
 1860 1865 1870

 Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser
 1875 1880 1885

 Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg
 1890 1895 1900

 His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile
 1905 1910 1915 1920

 Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro
 1925 1930 1935

 Glu Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Asn Leu Thr
 1940 1945 1950

 Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile Gly Ser Glu Cys
 1955 1960 1965

 Thr Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile
 1970 1975 1980

 Cys Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met
 1985 1990 1995 2000

 Pro Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Arg
 2005 2010 2015

 Gly Val Trp Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly

2020

2025

2030

Ala Glu Ile Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly
 2035 2040 2045

Pro Arg Thr Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala
 2050 2055 2060

Tyr Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Lys Phe
 2065 2070 2075 2080

Ala Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Arg Val
 2085 2090 2095

Gly Asp Phe His Tyr Val Ser Gly Met Thr Thr Asp Asn Leu Lys Cys
 2100 2105 2110

Pro Cys Gln Ile Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val
 2115 2120 2125

Arg Leu His Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu
 2130 2135 2140

Val Ser Phe Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu
 2145 2150 2155 2160

Pro Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr
 2165 2170 2175

Asp Pro Ser His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg
 2180 2185 2190

Gly Ser Pro Pro Ser Met Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala
 2195 2200 2205

Pro Ser Leu Lys Ala Thr Cys Thr Thr Asn His Asp Ser Pro Asp Ala
 2210 2215 2220

Glu Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn
 2225 2230 2235 2240

Ile Thr Arg Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe
 2245 2250 2255

Asp Pro Leu Val Ala Glu Glu Asp Glu Arg Glu Val Ser Val Pro Ala
 2260 2265 2270

Glu Ile Leu Arg Lys Ser Gln Arg Phe Ala Arg Ala Leu Pro Val Trp
 2275 2280 2285

Ala Arg Pro Asp Tyr Asn Pro Pro Leu Ile Glu Thr Trp Lys Glu Pro
 2290 2295 2300

Asp Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Arg
 2305 2310 2315 2320

Ser Pro Pro Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr
 2325 2330 2335
 Glu Ser Thr Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Lys Ser Phe
 2340 2345 2350
 Gly Ser Ser Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser
 2355 2360 2365
 Ser Glu Pro Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Val Glu Ser
 2370 2375 2380
 Tyr Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Phe
 2385 2390 2395 2400
 Ser Asp Gly Ser Trp Ser Thr Val Ser Ser Gly Ala Asp Thr Glu Asp
 2405 2410 2415
 Val Val Cys Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr
 2420 2425 2430
 Pro Cys Ala Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn
 2435 2440 2445
 Ser Leu Leu Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser
 2450 2455 2460
 Ala Cys Gln Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu
 2465 2470 2475 2480
 Asp Ser His Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ser
 2485 2490 2495
 Arg Val Lys Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr
 2500 2505 2510
 Pro Pro His Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val
 2515 2520 2525
 Arg Cys His Ala Arg Lys Ala Val Ala His Ile Asn Ser Val Trp Lys
 2530 2535 2540
 Asp Leu Leu Glu Asp Ser Val Thr Pro Ile Asp Thr Thr Ile Met Ala
 2545 2550 2555 2560
 Lys Asn Glu Val Phe Cys Val Gln Pro Glu Lys Gly Arg Lys Pro
 2565 2570 2575
 Ala Arg Leu Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys
 2580 2585 2590
 Met Ala Leu Tyr Asp Val Val Ser Lys Leu Pro Leu Ala Val Met Gly
 2595 2600 2605

Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu
2610 2615 2620

Val Gln Ala Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp
2625 2630 2635 2640

Thr Arg Cys Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu
2645 2650 2655

Glu Ala Ile Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala
2660 2665 2670

Ile Lys Ser Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn
2675 2680 2685

Ser Arg Gly Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val
2690 2695 2700

Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg
2705 2710 2715 2720

Ala Ala Cys Arg Ala Ala Gly Leu Gln Asp Arg Thr Met Leu Val Cys
2725 2730 2735

Gly Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp
2740 2745 2750

Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala
2755 2760 2765

Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr
2770 2775 2780

Ser Cys Ser Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg
2785 2790 2795 2800

Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala
2805 2810 2815

Trp Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile
2820 2825 2830

Ile Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His
2835 2840 2845

Phe Phe Ser Val Leu Ile Ala Arg Asp Gln Phe Glu Gln Ala Leu Asn
2850 2855 2860

Cys Glu Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro
2865 2870 2875 2880

Pro Ile Ile Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser
2885 2890 2895

Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu

2900

2905

2910

Gly Val Pro Pro Leu Arg Ala Trp Lys His Arg Ala Arg Ser Val Arg
 2915 2920 2925

Ala Arg Leu Leu Ser Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr
 2930 2935 2940

Leu Phe Asn Trp Ala Val Arg Thr Lys Pro Lys Leu Thr Pro Ile Ala
 2945 2950 2955 2960

Ala Ala Gly Arg Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser
 2965 2970 2975

Gly Gly Asp Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ser
 2980 2985 2990

Trp Phe Cys Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu
 2995 3000 3005

Pro Asn Arg
 3010

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3011 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn
 1 5 10 15

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gln Ile Val Gly
 20 25 30

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
 35 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
 50 55 60

Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly
 65 70 75 80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp
 85 90 95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro
 100 105 110

Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys
 115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu
 130 135 140

Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
 145 150 155 160

Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
 165 170 175

Phe Leu Leu Ala Leu Leu Ser Cys Leu Thr Val Pro Ala Ser Ala Tyr
 180 185 190

Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val Thr Asn Asp Cys Pro
 195 200 205

Asn Ser Ser Ile Val Tyr Glu Thr Ala Asp Thr Ile Leu His Ser Pro
 210 215 220

Gly Cys Val Pro Cys Val Arg Glu Gly Asn Thr Ser Lys Cys Trp Val
 225 230 235 240

Ala Val Ala Pro Thr Val Thr Arg Asp Gly Lys Leu Pro Ser Thr
 245 250 255

Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser Ala Thr Leu Cys
 260 265 270

Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Phe Leu Val Ser
 275 280 285

Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr Gln Asp Cys
 290 295 300

Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg Met Ala Trp
 305 310 315 320

Asp Met Met Met Asn Trp Ser Pro Thr Thr Ala Leu Val Val Ala Gln
 325 330 335

Leu Leu Arg Ile Pro Gln Ala Ile Leu Asp Met Ile Ala Gly Ala His
 340 345 350

Trp Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser Met Val Gly Asn Trp
 355 360 365

Ala Lys Val Leu Val Val Leu Leu Leu Phe Ser Gly Val Asp Ala Ala
 370 375 380

Thr Tyr Thr Thr Gly Gly Ser Val Ala Arg Thr Thr His Gly Leu Ser

385	390	395	400
Ser Leu Phe Ser Gln Gly Ala Lys Gln Asn Ile Gln Leu Ile Asn Thr			
405	410	415	
Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu Asn Cys Asn Ala Ser			
420	425	430	
Leu Asp Thr Gly Trp Val Ala Gly Leu Phe Tyr Tyr His Lys Phe Asn			
435	440	445	
Ser Ser Gly Cys Pro Glu Arg Met Ala Ser Cys Arg Pro Leu Ala Asp			
450	455	460	
Phe Asp Gln Gly Trp Gly Pro Ile Ser Tyr Thr Asn Gly Ser Gly Pro			
465	470	475	480
Glu His Arg Pro Tyr Cys Trp His Tyr Pro Pro Lys Pro Cys Gly Ile			
485	490	495	
Val Pro Ala Gln Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro Ser			
500	505	510	
Pro Val Val Val Gly Thr Thr Asp Lys Ser Gly Ala Pro Thr Tyr Thr			
515	520	525	
Trp Gly Ser Asn Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg Pro			
530	535	540	
Pro Pro Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser Ser Gly Phe			
545	550	555	560
Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly Ala Gly Asn			
565	570	575	
Asn Thr Leu His Cys Pro Thr Asp Cys Phe Arg Lys His Pro Glu Ala			
580	585	590	
Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg Cys Leu			
595	600	605	
Val His Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile Asn Tyr			
610	615	620	
Thr Leu Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu His Arg Leu			
625	630	635	640
Glu Val Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu Asp Asp			
645	650	655	
Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Ser Thr Thr Gln Trp			
660	665	670	
Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Thr Thr Gly			
675	680	685	

Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu Tyr Gly
 690 695 700
 Val Gly Ser Ser Ile Val Ser Trp Ala Ile Lys Trp Glu Tyr Val Ile
 705 710 715 720
 Leu Leu Phe Leu Leu Ala Asp Ala Arg Ile Cys Ser Cys Leu Trp
 725 730 735
 Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu Asn Leu Val
 740 745 750
 Leu Leu Asn Ala Ala Ser Leu Ala Gly Thr His Gly Leu Val Ser Phe
 755 760 765
 Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly Lys Trp Val Pro
 770 775 780
 Gly Val Ala Tyr Ala Phe Tyr Gly Met Trp Pro Phe Leu Leu Leu Leu
 785 790 795 800
 Leu Ala Leu Pro Gln Arg Ala Tyr Ala Leu Asp Thr Glu Met Ala Ala
 805 810 815
 Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala Leu Thr Leu Ser
 820 825 830
 Pro His Tyr Lys Arg Tyr Ile Cys Trp Cys Val Trp Trp Leu Gln Tyr
 835 840 845
 Phe Leu Thr Arg Ala Glu Ala Leu Leu His Gly Trp Val Pro Pro Leu
 850 855 860
 Asn Val Arg Gly Gly Arg Asp Ala Val Ile Leu Leu Met Cys Val Val
 865 870 875 880
 His Pro Ala Leu Val Phe Asp Ile Thr Lys Leu Leu Leu Ala Val Leu
 885 890 895
 Gly Pro Leu Trp Ile Leu Gln Thr Ser Leu Leu Lys Val Pro Tyr Phe
 900 905 910
 Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu Ala Arg Lys Met
 915 920 925
 Ala Gly Gly His Tyr Val Gln Met Val Thr Ile Lys Met Gly Ala Leu
 930 935 940
 Ala Gly Thr Tyr Val Tyr Asn His Leu Thr Pro Leu Arg Asp Trp Ala
 945 950 955 960
 His Asn Gly Leu Arg Asp Leu Ala Val Ala Val Glu Pro Val Val Phe
 965 970 975

Ser Gln Met Glu Thr Lys Leu Ile Thr Trp Gly Ala Asp Thr Ala Ala
980 985 990

Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala Arg Arg Gly Arg
995 1000 1005

Glu Ile Leu Leu Gly Pro Ala Asp Gly Met Val Ser Lys Gly Trp Arg
1010 1015 1020

Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr Arg Gly Leu Leu
1025 1030 1035 1040

Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu
1045 1050 1055

Gly Glu Val Gln Ile Val Ser Thr Ala Ala Gln Thr Phe Leu Ala Thr
1060 1065 1070

Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Thr Arg
1075 1080 1085

Thr Ile Ala Ser Pro Lys Gly Pro Val Ile Gln Met Tyr Thr Asn Val
1090 1095 1100

Asp Arg Asp Leu Val Gly Trp Pro Ala Pro Gln Gly Ala Arg Ser Leu
1105 1110 1115 1120

Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His
1125 1130 1135

Ala Asp Val Ile Pro Val Arg Arg Gly Asp Ser Arg Gly Ser Leu
1140 1145 1150

Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro
1155 1160 1165

Leu Leu Cys Pro Ala Gly His Ala Val Gly Ile Phe Arg Ala Ala Val
1170 1175 1180

Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Ile Pro Val Glu Ser
1185 1190 1195 1200

Leu Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro
1205 1210 1215

Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr
1220 1225 1230

Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly
1235 1240 1245

Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe
1250 1255 1260

Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr

1265	1270	1275	1280
Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr			
1285	1290	1295	
Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile			
1300	1305	1310	
Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly			
1315	1320	1325	
Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val			
1330	1335	1340	
Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro			
1345	1350	1355	1360
Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr			
1365	1370	1375	
Gly Lys Ala Ile Pro Leu Glu Ala Ile Lys Gly Gly Arg His Leu Ile			
1380	1385	1390	
Phe Cys His Ser Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val			
1395	1400	1405	
Thr Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser			
1410	1415	1420	
Val Ile Pro Thr Ser Gly Asp Val Val Val Ala Thr Asp Ala Leu			
1425	1430	1435	1440
Met Thr Gly Phe Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr			
1445	1450	1455	
Cys Val Thr Gln Ala Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile			
1460	1465	1470	
Glu Thr Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg			
1475	1480	1485	
Gly Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro			
1490	1495	1500	
Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys			
1505	1510	1515	1520
Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr			
1525	1530	1535	
Val Arg Leu Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln			
1540	1545	1550	
Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile			
1555	1560	1565	

Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro
 1570 1575 1580
 Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro
 1585 1590 1595 1600
 Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro
 1605 1610 1615
 Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln
 1620 1625 1630
 Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Thr Cys
 1635 1640 1645
 Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly
 1650 1655 1660
 Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val
 1665 1670 1675 1680
 Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro Ala Ile Ile Pro
 1685 1690 1695
 Asp Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser
 1700 1705 1710
 Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe
 1715 1720 1725
 Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser His Gln Ala Glu
 1730 1735 1740
 Val Ile Ala Pro Ala Val Gln Thr Asn Trp Gln Arg Leu Glu Thr Phe
 1745 1750 1755 1760
 Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala
 1765 1770 1775
 Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala
 1780 1785 1790
 Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu
 1795 1800 1805
 Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Ser
 1810 1815 1820
 Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly
 1825 1830 1835 1840
 Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu Ala Gly Tyr Gly
 1845 1850 1855

Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu
 1860 1865 1870

Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser
 1875 1880 1885

Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg
 1890 1895 1900

His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile
 1905 1910 1915 1920

Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro
 1925 1930 1935

Gly Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr
 1940 1945 1950

Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Val Ser Ser Glu Cys
 1955 1960 1965

Thr Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile
 1970 1975 1980

Cys Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met
 1985 1990 1995 2000

Pro Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys
 2005 2010 2015

Gly Val Trp Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly
 2020 2025 2030

Ala Glu Ile Ala Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly
 2035 2040 2045

Pro Lys Thr Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala
 2050 2055 2060

Tyr Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Lys Phe
 2065 2070 2075 2080

Ala Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val
 2085 2090 2095

Gly Asp Phe His Tyr Val Thr Gly Met Thr Ala Asp Asn Leu Lys Cys
 2100 2105 2110

Pro Cys Gln Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val
 2115 2120 2125

Arg Leu His Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Asp Glu
 2130 2135 2140

Val Ser Phe Arg Val Gly Leu His Asp Tyr Pro Val Gly Ser Gln Leu

2145	2150	2155	2160
Pro Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr			
2165		2170	2175
Asp Pro Ser His Ile Thr Ala Glu Thr Ala Gly Arg Arg Leu Ala Arg			
2180	2185	2190	
Gly Ser Pro Pro Ser Met Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala			
2195	2200	2205	
Pro Ser Leu Lys Ala Thr Cys Thr Thr Asn His Asp Ser Pro Asp Ala			
2210	2215	2220	
Glu Leu Leu Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn			
2225	2230	2235	2240
Ile Thr Arg Val Glu Ser Glu Asn Lys Val Val Val Leu Asp Ser Phe			
2245	2250	2255	
Asp Pro Leu Val Ala Glu Glu Asp Glu Arg Glu Val Ser Val Pro Ala			
2260	2265	2270	
Glu Ile Leu Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Ser Trp			
2275	2280	2285	
Ala Arg Pro Asp Tyr Asn Pro Pro Leu Leu Glu Thr Trp Lys Lys Pro			
2290	2295	2300	
Asp Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Gln			
2305	2310	2315	2320
Ser Pro Pro Val Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr			
2325	2330	2335	
Glu Ser Thr Val Ser Ser Ala Leu Ala Glu Leu Ala Thr Lys Ser Phe			
2340	2345	2350	
Gly Ser Ser Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser			
2355	2360	2365	
Ser Glu Pro Ala Pro Ser Val Cys Pro Pro Asp Ser Asp Ala Glu Ser			
2370	2375	2380	
Tyr Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu			
2385	2390	2395	2400
Ser Asp Gly Ser Trp Ser Thr Val Ser Ser Gly Ala Asp Thr Glu Asp			
2405	2410	2415	
Val Val Cys Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Ile Thr			
2420	2425	2430	
Pro Cys Ala Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn			
2435	2440	2445	

Ser Leu Leu Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Asn
 2450 2455 2460

 Ala Cys Leu Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu
 2465 2470 2475 2480

 Asp Asn His Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser
 2485 2490 2495

 Lys Val Lys Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr
 2500 2505 2510

 Pro Pro His Ser Ala Arg Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val
 2515 2520 2525

 Arg Cys His Ala Arg Lys Ala Val Ser His Ile Asn Ser Val Trp Lys
 2530 2535 2540

 Asp Leu Leu Glu Asp Ser Val Thr Pro Ile Asp Thr Thr Ile Met Ala
 2545 2550 2555 2560

 Lys Asn Glu Val Phe Cys Val Gln Pro Glu Lys Gly Arg Lys Pro
 2565 2570 2575

 Ala Arg Leu Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys
 2580 2585 2590

 Met Ala Leu Tyr Asp Val Val Ser Lys Leu Pro Leu Ala Val Met Gly
 2595 2600 2605

 Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu
 2610 2615 2620

 Val Gln Ala Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp
 2625 2630 2635 2640

 Thr Arg Cys Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu
 2645 2650 2655

 Glu Ala Ile Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala
 2660 2665 2670

 Ile Lys Ser Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn
 2675 2680 2685

 Ser Arg Gly Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val
 2690 2695 2700

 Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg
 2705 2710 2715 2720

 Ala Ala Cys Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys
 2725 2730 2735

Gly Asp Asp Leu Val Val Ile Cys Glu Ser Gln Gly Val Gln Glu Asp
 2740 2745 2750
 Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala
 2755 2760 2765
 Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr
 2770 2775 2780
 Pro Cys Ser Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg
 2785 2790 2795 2800
 Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala
 2805 2810 2815
 Trp Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile
 2820 2825 2830
 Ile Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His
 2835 2840 2845
 Phe Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp
 2850 2855 2860
 Cys Glu Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro
 2865 2870 2875 2880
 Pro Ile Ile Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser
 2885 2890 2895
 Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu
 2900 2905 2910
 Gly Val Pro Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg
 2915 2920 2925
 Ala Arg Leu Leu Ser Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr
 2930 2935 2940
 Leu Phe Asn Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala
 2945 2950 2955 2960
 Ala Ala Gly Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Gly
 2965 2970 2975
 Gly Gly Asp Ile Tyr His Ser Val Ser Arg Ala Arg Pro Arg Trp Phe
 2980 2985 2990
 Trp Phe Cys Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu
 2995 3000 3005
 Pro Asn Arg
 3010

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7298 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 922..2532

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GACGGATCGG GAGATCTCCC GATCCCCTAT GGTCGACTCT CAGTACAATC TGCTCTGATG	60		
CCGCATAGTT AAGCCAGTAT CTGCTCCCTG CTTGTGTGTT GGAGGTCGCT GAGTAGTGCG	120		
CGAGCAAAAT TTAAGCTACA ACAAGGCAAG GCTTGACCGA CAATTGCAATG AAGAATCTGC	180		
TTAGGGTTAG CGGTTTTGCG CTGCTTCGCG ATGTACGGGC CAGATATACT CGTTGACATT	240		
GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGTC ATTAGTTCAT AGCCCATATA	300		
TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC	360		
CCCGCCCCATT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC	420		
ATTGACGTCA ATGGGTGGAC TATTTACGGT AACTGCCA CTTGGCAGTA CATCAAGTGT	480		
ATCATATGCC AAGTACGCC CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT	540		
ATGCCAGTA CATGACCTTA TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA	600		
TCGCTATTAC CATGGTATG CGGTTTTGGC AGTACATCAA TGGCGTGGA TAGCGGTTTG	660		
ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA TGGGAGTTTG TTTTGGCACC	720		
AAAATCAACG GGACTTTCCA AAATGTCGTA ACAACTCCGC CCCATTGACG CAAATGGCG	780		
GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA	840		
CTGCTTAACT GGCTTATCGA AATTAATACG ACTCACTATA GGGAGACCGG AAGCTTTGCT	900		
CTAGACTGGG ATTGGGGCGC G ATG CTG CCC GGT TTG GCA CTG CTC CTG CTG	951		
Met Leu Pro Gly Leu Ala Leu Leu Leu Leu			
1	5	10	
GCC GCC TGG ACG GCT CGG GCG CTG GAG GTA CCC ACT GAT GGT AAT GCT			999
Ala Ala Trp Thr Ala Arg Ala Leu Glu Val Pro Thr Asp Gly Asn Ala			

GGC CTG CTG GCT GAA CCC CAG ATT GCC ATG TTC TGT GGC AGA CTG AAC 1047
 Gly Leu Leu Ala Glu Pro Gln Ile Ala Met Phe Cys Gly Arg Leu Asn
 30 35 40
 ATG CAC ATG AAT GTC CAG AAT GGG AAG TGG GAT TCA GAT CCA TCA GGG 1095
 Met His Met Asn Val Gln Asn Gly Lys Trp Asp Ser Asp Pro Ser Gly
 45 50 55
 ACC AAA ACC TGC ATT GAT ACC AAG GAA ACC CAC GTC ACC GGG GGA AGT 1143
 Thr Lys Thr Cys Ile Asp Thr Lys Glu Thr His Val Thr Gly Gly Ser
 60 65 70
 GCC GGC CAC ACC ACG GCT GGG CTT CGT CTC CTT TCA CCA GGC GCC 1191
 Ala Gly His Thr Thr Ala Gly Leu Val Arg Leu Leu Ser Pro Gly Ala
 75 80 85 90
 AAG CAG AAC ATC CAA CTG ATC AAC ACC AAC GGC AGT TGG CAC ATC AAT 1239
 Lys Gln Asn Ile Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn
 95 100 105
 AGC ACG GCC TTG AAC TGC AAT GAA AGC CTT AAC ACC GGC TGG TTA GCA 1287
 Ser Thr Ala Leu Asn Cys Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala
 110 115 120
 GGG CTC TTC TAT CAC CAC AAA TTC AAC TCT TCA GGT TGT CCT GAG AGG 1335
 Gly Leu Phe Tyr His His Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg
 125 130 135
 TTG GCC AGC TGC CGA CGC CTT ACC GAT TTT GCC CAG GGC GGG GGT CCT 1383
 Leu Ala Ser Cys Arg Arg Leu Thr Asp Phe Ala Gln Gly Gly Gly Pro
 140 145 150
 ATC AGT TAC GCC AAC GGA AGC GGC CTC GAT GAA CGC CCC TAC TGC TGG 1431
 Ile Ser Tyr Ala Asn Gly Ser Gly Leu Asp Glu Arg Pro Tyr Cys Trp
 155 160 165 170
 CAC TAC CCT CCA AGA CCT TGT GGC ATT GTG CCC GCA AAG AGC GTG TGT 1479
 His Tyr Pro Pro Arg Pro Cys Gly Ile Val Pro Ala Lys Ser Val Cys
 175 180 185
 GGC CCG GTA TAT TGC TTC ACT CCC AGC CCC GTG GTG GTG GGA ACG ACC 1527
 Gly Pro Val Tyr Cys Phe Thr Pro Ser Pro Val Val Val Gly Thr Thr
 190 195 200
 GAC AGG TCG GGC GCG CCT ACC TAC AGC TGG GGT GCA AAT GAT ACG GAT 1575
 Asp Arg Ser Gly Ala Pro Thr Tyr Ser Trp Gly Ala Asn Asp Thr Asp
 205 210 215
 GTC TTT GTC CTT AAC ACC AGG CCA CCG CTG GGC AAT TGG TTC GGT 1623
 Val Phe Val Leu Asn Asn Thr Arg Pro Pro Leu Gly Asn Trp Phe Gly
 220 225 230
 TGC ACC TGG ATG AAC TCA ACT GGA TTC ACC AAA GTG TGC GGA GCG CCC 1671
 Cys Thr Trp Met Asn Ser Thr Gly Phe Thr Lys Val Cys Gly Ala Pro
 235 240 245 250

CCT TGT GTC ATC GGA GGG GTG GGC AAC AAC ACC TTG CTC TGC CCC ACT Pro Cys Val Ile Gly Gly Val Gly Asn Asn Thr Leu Leu Cys Pro Thr 255 260 265	1719
GAT TGC TTC CGC AAG CAT CCG GAA GCC ACA TAC TCT CCG TGC GGC TCC Asp Cys Phe Arg Lys His Pro Glu Ala Thr Tyr Ser Arg Cys Gly Ser 270 275 280	1767
GGT CCC TGG ATT ACA CCC AGG TGC ATG GTC GAC TAC CCG TAT AGG CTT Gly Pro Trp Ile Thr Pro Arg Cys Met Val Asp Tyr Pro Tyr Arg Leu 285 290 295	1815
TGG CAC TAT CCT TGT ACC ATC AAT TAC ACC ATA TTC AAA GTC AGG ATG Trp His Tyr Pro Cys Thr Ile Asn Tyr Thr Ile Phe Lys Val Arg Met 300 305 310	1863
TAC GTG GGA GGG GTC GAG CAC AGG CTG GAA GCG GCC TGC AAC TGG ACG Tyr Val Gly Gly Val Glu His Arg Leu Glu Ala Ala Cys Asn Trp Thr 315 320 325 330	1911
CGG GGC GAA CGC TGT GAT CTG GAA GAC AGG GAC AGG TCC GAG CTC AGC Arg Gly Glu Arg Cys Asp Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser 335 340 345	1959
CCG TTA CTG CTG TCC ACC ACG CAG TGG CAG GTC CTT CCG TGT TCT TTC Pro Leu Leu Leu Ser Thr Thr Gln Trp Gln Val Leu Pro Cys Ser Phe 350 355 360	2007
ACG ACC CTG CCA GCC TTG TCC ACC GGC CTC ATC CAC CTC CAC CAG AAC Thr Thr Leu Pro Ala Leu Ser Thr Gly Leu Ile His Leu His Gln Asn 365 370 375	2055
ATT GTG GAC GTG CAG TAC TTG TAC GGG GTA GGG TCA AGC ATC GCG TCC Ile Val Asp Val Gln Tyr Leu Tyr Gly Val Gly Ser Ser Ile Ala Ser 380 385 390	2103
TGG GCT ATT AAG TCG GAG TAC GAC GTT CTC CTG TTC CTT CTG CTT GCA Trp Ala Ile Lys Trp Glu Tyr Asp Val Leu Leu Phe Leu Leu Ala 395 400 405 410	2151
GAC GCG CGC GTT TGC TCC TGC TTG TGG ATG ATG TTA CTC ATA TCC CAA Asp Ala Arg Val Cys Ser Cys Leu Trp Met Met Leu Leu Ile Ser Gln 415 420 425	2199
GCG GAG GCG GCT TTG GAG ATC TCT GAA GTG AAG ATG GAT GCA GAA TTC Ala Glu Ala Ala Leu Glu Ile Ser Glu Val Lys Met Asp Ala Glu Phe 430 435 440	2247
CGA CAT GAC TCA GGA TAT GAA GTT CAT CAT CAA AAA TTG GTG TTC TTT Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys Leu Val Phe Phe 445 450 455	2295
GCA GAA GAT GTG GGT TCA AAC AAA GGT GCA ATC ATT GGA CTC ATG GTG Ala Glu Asp Val Gly Ser Asn Lys Gly Ala Ile Ile Gly Leu Met Val	2343

460	465	470	
GGC GGT GTT GTC ATA GCG ACA GTG ATC GTC ATC ACC TTG GTG ATG CTG Gly Gly Val Val Ile Ala Thr Val Ile Val Ile Thr Leu Val Met Leu 475 480 485 490			2391
AAG AAG AAA CAG TAC ACA TCC ATT CAT CAT GGT GTG GTG GAG GTT GAC Lys Lys Lys Gln Tyr Thr Ser Ile His His Gly Val Val Glu Val Asp 495 500 505			2439
GCC GCT GTC ACC CCA GAG GAG CGC CAC CTG TCC AAG ATG CAG CAG AAC Ala Ala Val Thr Pro Glu Glu Arg His Leu Ser Lys Met Gln Gln Asn 510 515 520			2487
GGC TAC GAA AAT CCA ACC TAC AAG TTC TTT GAG CAG ATG CAG AAC Gly Tyr Glu Asn Pro Thr Tyr Lys Phe Phe Glu Gln Met Gln Asn 525 530 535			2532
TAGACCCCCG CCACAGCAGC CTCTGAAGTT GGACAGCAAA ACCATTGCTT CACTACCCAT 2592			
CGGTGTCCAT TTATAGAATA ATGTGGGAAG AAACAAACCC GTTTTATGAT TTACTCATTA 2652			
TCGCCTTTG ACAGCTGTGC TGTAACACAA GTAGATGCCT GAACTTGAAT TAATCCACAC 2712			
ATCAGTATTG TATTCTATCT CTCTTTACAT TTTGGTCTCT ATACTACATT ATTAATGGGT 2772			
TTTGTGTACT GTAAAGAATT TAGCTGTATC AAACTAGTGC ATGAATAGGC CGCTCGAGCA 2832			
TGCATCTAGA GGGCCCTATT CTATAGTGTG ACCTAAATGC TCGCTGATCA GCCTCGACTG 2892			
TGCCTTCTAG TTGCCAGCCA TCTGTTGTTT GCCCCTCCCC CGTGCCTTCC TTGACCCCTGG 2952			
AAGGTGCCAC TCCCCTGTG CTTTCTTAAT AAAATGAGGA AATTGCATCG CATTGTCTGA 3012			
GTAGGTGTCA TTCTATTCTG GGGGGTGGGG TGGGGCAGGA CAGCAAGGGG GAGGATTGGG 3072			
AAGACAATAG CAGGCATGCT GGGGATGCGG TGGGCTCTAT GGAACCAGCT GGGGCTCGAG 3132			
GGGGGATCCC CACGCGCCCT GTAGCGGCGC ATTAAGCGCG GCGGGTGTGG TGGTTACGCG 3192			
CAGCGTGACC GCTACACTTG CCAGCGCCCT AGCGCCCGCT CCTTTCGCTT TCTTCCCTTC 3252			
CTTTCTCGCC ACGTTCGCCG GCTTTCCCG TCAAGCTCTA AATCGGGGCA TCCCTTTAGG 3312			
GTTCCGATTT AGTGCTTAC GGACACCTCGA CCCCCAAAAAA CTTGATTAGG GTGATGGTTC 3372			
ACGTAGTGGG CCATCGCCCT GATAGACGGT TTTTCGCTT TACTGAGCAC TCTTTAATAG 3432			
TGGACTCTTG TTCCAAACTG GAACAACACT CAACCCTATC TCGGTCTATT CTTTTGATTT 3492			
ATAAGATTTC CATGCCATG TAAAAGTGTG ACAATTAGCA TTAAATTACT TCTTTATATG 3552			
CTACTATTCT TTTGGCTTCG TTCACGGGGT GGGTACCGAG CTCGAATTCT GTGGAATGTG 3612			
TGTCAGTTAG GGTGTGGAAA GTCCCCAGGC TCCCCAGGCA GGCAAGTA TGCAAAGCAT 3672			

GCATCTCAAT TAGTCAGCAA CCAGGTGTGG AAAGTCCCCA GGCTCCCCAG CAGGCAGAAG	3732
TATGCAAAGC ATGCATCTCA AT TTT AGC AACCATAGTC CCGCCCCCTAA CTCCGCCCCAT	3792
CCCGCCCCCTA ACTCCGCCA GTTCCGCCA TTCTCCGCC CATGGCTGAC TAATTTTTT	3852
TATTTATGCA GAGGCCGAGG CCGCCTCGGC CTCTGAGCTA TTCCAGAAGT AGTGAGGAGG	3912
CTTTTTTGGGA GGCCTAGGCT TTTGCAAAAA GCTCCCGGGA GCTTGGATAT CCATTTTCGG	3972
ATCTGATCAA GAGACAGGAT GAGGATCGTT TCGCATGATT GAACAAGATG GATTGCACGC	4032
AGGTTCTCCG GCCGCTTGGG TGGAGAGGCT ATTGGCTAT GACTGGGCAC AACAGACAAT	4092
CGGCTGCTCT GATGCCGCCG TGTTCCGGCT GTCAGCGCAG GGGCGCCCGG TTCTTTTGT	4152
CAAGACCGAC CTGTCCGGTG CCCTGAATGA ACTGCAGGAC GAGGCAGCGC GGCTATCGT	4212
GCTGGCCACG ACGGGCGTTC CTTGCGCAGC TGTGCTCGAC GTTGTCACTG AAGCGGGAAAG	4272
GGACTGGCTG CTATTGGCG AAGTGCCGGG GCAGGATCTC CTGTCATCTC ACCTTGCTCC	4332
TGCCGAGAAA GTATCCATCA TGGCTGATGC AATGCCGGG CTGCATACGC TTGATCCGGC	4392
TACCTGCCA TTGGACCACC AAGCGAAACA TCGCATCGAG CGAGCACGTA CTCGGATGGA	4452
AGCCGGTCTT GTCGATCAGG ATGATCTGGA CGAAGACCAT CAGGGGCTCG CGCCAGCCGA	4512
ACTGTTGCC AGGCTCAAGG CGCGCATGCC CGACGGCGAG GATCTCGTCG TGACCCATGG	4572
CGATGCCTGC TTGCCGAATA TCATGGTGGAA AAATGCCGC TTTCTGGAT TCATCGACTG	4632
TGGCCGGCTG GGTGTGGCGG ACCGCTATCA GGACATAGCG TTGGCTACCC GTGATATTGC	4692
TGAAGAGCTT GGCGCGAAT GGGCTGACCG CTTCTCGTG CTTTACGGTA TCGCCGCTCC	4752
CGATTGCGAG CGCATCGCCT TCTATGCCCT TCTTGACGAG TTCTCTGAG CGGGACTCTG	4812
GGGTTCGAAA TGACCGACCA AGCGACGCC AACCTGCCAT CACGAGATTT CGATTCCACC	4872
GCCGCCTCT ATGAAAGGTT GGGCTTCGGA ATCGTTTCC GGGACGCCGG CTGGATGATC	4932
CTCCAGGCCG GGGATCTCAT GCTGGAGTTC TTGCCCCACC CCAACTTGTGTT TATTGCAGCT	4992
TATAATGGTT ACAAAATAAG CAATAGCATC ACAAAATTCA CAAATAAAGC ATTTTTTCA	5052
CTGCATTCTA GTTGTGGTTT GTCCAAACTC ATCAATGTAT CTTATCATGT CTGGATCCCG	5112
TCGACCTCGA GAGCTTGGCG TAATCATGGT CATACTGTGTT TCCTGTGTGA AATTGTTATC	5172
CGCTCACAAT TCCACACAAAC ATACGAGCCG GAAGCATAAA GTGTAAAGCC TGGGGTGCCT	5232
AATGAGTGAG CTAACTCACA TTAATTGCGT TGGCCTCACT GCCCGCTTTC CAGTCGGAA	5292

ACCTGTCGTG CCAGCTGCAT TAATGAATCG GCCAACGCGC GGGGAGAGGC GGTTTGCATA	5352
TTGGCGCTC TTCCGCTTCC TCGCTCACTG ACTCGCTGCG CTCGGTCGTT CGGCTGCGGC	5412
GAGCGGTATC AGCTCACTCA AAGGCGGTAA TACGGTTATC CACAGAATCA GGGGATAACG	5472
CAGGAAAGAA CATGTGAGCA AAAGGCCAGC AAAAGGCCAG GAACCGTAAA AAGGCCGCGT	5532
TGCTGGCGTT TTTCCATAGG CTCCGCCCCC CTGACGAGCA TCACAAAAAT CGACGCTCAA	5592
GTCAGAGGTG GCGAAACCCG ACAGGACTAT AAAGATACCA GGC GTTCCC CCTGGAAGCT	5652
CCCTCGTGC CGCTCCTGTT CCGACCCCTGC CGCTTACCGG ATACCTGTCC GCCTTCTCC	5712
CTTCGGGAAG CGTGGCGCTT TCTCAATGCT CACGCTGTAG GTATCTCAGT TCGGTGTAAG	5772
TCGTTCGCTC CAAGCTGGGC TGTGTGCACG AACCCCCCGT TCAGCCGAC CGCTGCGCCT	5832
TATCCGGTAA CTATCGTCTT GAGTCCAACC CGGTAAGACA CGACTTATCG CCACTGGCAG	5892
CAGCCACTGG TAACAGGATT AGCAGAGCGA GGTATGTAAG CGGTGCTACA GAGTTCTTGA	5952
AGTGGTGGCC TAACTACGGC TACACTAGAA CGACAGTATT TGCTATCTGC GCTCTGCTGA	6012
AGCCAGTTAC CTT CGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAACAA ACCACCGCTG	6072
GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACCGC CAGAAAAAAA GGATCTCAAG	6132
AAGATCCTTT GATCTTTCT ACGGGGTCTG ACGCTCAGTG GAACGAAAAC TCACGTTAAG	6192
GGATTTGGT CATGAGATTA TCAAAAAGGA TCTTCACCTA GATCCTTTA AATTAAAAAT	6252
GAAGTTTAA ATCAATCTAA AGTATATATG AGTAAACTTG GTCTGACAGT TACCAATGCT	6312
TAATCAGTGA GGCACCTATC TCAGCGATCT GTCTATTTCG TTCATCCATA GTTGCCTGAC	6372
TCCCCGTCGT GTAGATAACT ACGATAACGGG AGGGCTTACCG ATCTGGCCCC AGTGCCTGCAA	6432
TGATACCGCG AGACCCACGC TCACCGGCTC CAGATTTATC AGCAATAAAC CAGCCAGCCG	6492
GAAGGGCCGA GCGCAGAAGT GGTCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT	6552
GTTGCCGGGA AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGAAC GTTGTGCCA	6612
TTGCTACAGG CATCGTGGTG TCACCGCTCGT CGTTGGTAT GGCTTCATTG AGCTCCGGTT	6672
CCCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG CAAAAAAGCG GTTAGCTCCT	6732
TCGGTCCTCC GATCGTTGTC AGAAGTAAGT TGGCCGCAGT GTTATCACTC ATGGTTATGG	6792
CAGCACTGCA TAATTCTCTT ACTGTCAATGC CATCCGTAAG ATGCTTTCT GTGACTGGTG	6852
AGTACTCAAC CAAGTCATTG TGAGAATAGT GTATGCGCG ACCGAGTTGC TCTTGCCCCG	6912
CGTCAATACG GGATAATACC GCGCCACATA GCAGAACTTT AAAAGTGCTC ATCATGGAA	6972

AACGTTCTTC GGGCGAAAAA CTCTCAAGGA TCTTACCGCT GTTGAGATCC AGTTCGATGT	7032
AACCCACTCG TGCACCCAAC TGATCTTCAG CATCTTTTAC TTTCACCCAGC GTTTCTGGGT	7092
GAGAAAAAC AGGAAGGCAA AATGCCGCAA AAAAGGGAAT AAGGGCGACA CGGAAATGTT	7152
GAATACTCAT ACTCTTCCTT TTTCAATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA	7212
TGAGCGGATA CATATTTGAA TGTATTAGA AAAATAAACAA AATAGGGGTT CCGCGCACAT	7272
TTCCCCGAAA AGTGCCACCT GACGTC	7298

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 537 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Leu Pro Gly Leu Ala Leu Leu Leu Ala Ala Trp Thr Ala Arg			
1	5	10	15
Ala Leu Glu Val Pro Thr Asp Gly Asn Ala Gly Leu Leu Ala Glu Pro			
20	25	30	
Gln Ile Ala Met Phe Cys Gly Arg Leu Asn Met His Met Asn Val Gln			
35	40	45	
Asn Gly Lys Trp Asp Ser Asp Pro Ser Gly Thr Lys Thr Cys Ile Asp			
50	55	60	
Thr Lys Glu Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala			
65	70	75	80
Gly Leu Val Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu			
85	90	95	
Ile Asn Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys			
100	105	110	
Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His			
115	120	125	
Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg			
130	135	140	
Leu Thr Asp Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly			
145	150	155	160

Ser Gly Leu Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Pro
165 170 175

Cys Gly Ile Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe
180 185 190

Thr Pro Ser Pro Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro
195 200 205

Thr Tyr Ser Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu Asn Asn
210 215 220

Thr Arg Pro Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser
225 230 235 240

Thr Gly Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly
245 250 255

Val Gly Asn Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys His
260 265 270

Pro Glu Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro
275 280 285

Arg Cys Met Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr
290 295 300

Ile Asn Tyr Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu
305 310 315 320

His Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp
325 330 335

Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu Ser Thr
340 345 350

Thr Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu
355 360 365

Ser Thr Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr
370 375 380

Leu Tyr Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu
385 390 395 400

Tyr Asp Val Leu Leu Phe Leu Leu Ala Asp Ala Arg Val Cys Ser
405 410 415

Cys Leu Trp Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu
420 425 430

Ile Ser Glu Val Lys Met Asp Ala Glu Phe Arg His Asp Ser Gly Tyr
435 440 445

Glu Val His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser

450	455	460
Asn Lys Gly Ala Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala		
465	470	475
Thr Val Ile Val Ile Thr Leu Val Met Leu Lys Lys Lys Gln Tyr Thr		
485	490	495
Ser Ile His His Gly Val Val Glu Val Asp Ala Ala Val Thr Pro Glu		
500	505	510
Glu Arg His Leu Ser Lys Met Gln Gln Asn Gly Tyr Glu Asn Pro Thr		
515	520	525
Tyr Lys Phe Phe Glu Gln Met Gln Asn		
530	535	

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7106 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 922..2022

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GACGGATCGG GAGATCTCCC GATCCCCTAT GGTCGACTCT CAGTACAATC TGCTCTGATG	60
CCGCATAGTT AAGCCAGTAT CTGCTCCCTG CTTGTGTGTT GGAGGTCGCT GAGTAGTGC	120
CGAGCAAAAT TTAAGCTACA ACAAGGCAAG GCTTGACCGA CAATTGCATG AAGAATCTGC	180
TTAGGGTTAG GCGTTTGCG CTGCTTCGCG ATGTACGGGC CAGATATACT CGTTGACATT	240
GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGTC ATTAGTTCAT AGCCCATATA	300
TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC	360
CCCGCCCATT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA CGGACTTTCC	420
ATTGACGTCA ATGGGTGGAC TATTTACGGT AACTGCCA CTTGGCAGTA CATCAAGTGT	480
ATCATATGCC AAGTACGCC CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT	540
ATGCCAGTA CATGACCTTA TGGGACTTTC CTACTGGCA GTACATCTAC GTATTAGTCA	600

TCGCTATTAC CATGGTGATG CGGTTTGGC AGTACATCAA TGGCGTGGA TAGCGTTTG	660
ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA TGGAGTTTG TTTTGGCACC	720
AAAATCAACG GGACTTTCCA AAATGTCGTA ACAACTCCGC CCCATTGACG CAAATGGCG	780
GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCA	840
CTGCTTAACT GGCTTATCGA AATTAATACG ACTCACTATA GGGAGACCGG AAGCTTGCT	900
CTAGACTGGA ATTGGGGCGC G ATG CTG CCC GGT TTG GCA CTG CTC CTG CTG Met Leu Pro Gly Leu Ala Leu Leu Leu Leu	951
1 5 10	
GCC GCC TGG ACG GCT CGG GCG CTG GAG GTA CCC ACT GAT GGT AAT GCT Ala Ala Trp Thr Ala Arg Ala Leu Glu Val Pro Thr Asp Gly Asn Ala	999
15 20 25	
GGC CTG CTG GCT GAA CCC CAG ATT GCC ATG TTC TGT GGC AGA CTG AAC Gly Leu Leu Ala Glu Pro Gln Ile Ala Met Phe Cys Gly Arg Leu Asn	1047
30 35 40	
ATG CAC ATG AAT GTC CAG AAT GGG AAG TGG GAT TCA GAT CCA TCA GGG Met His Met Asn Val Gln Asn Gly Lys Trp Asp Ser Asp Pro Ser Gly	1095
45 50 55	
ACC AAA ACC TGC ATT GAT ACC AAG GAA ACC CAC GTC ACC GGG GGA AGT Thr Lys Thr Cys Ile Asp Thr Lys Glu Thr His Val Thr Gly Gly Ser	1143
60 65 70	
GCC GGC CAC ACC ACG GCT GGG CTT GTT CGT CTC CTT TCA CCA GGC GCC Ala Gly His Thr Thr Ala Gly Leu Val Arg Leu Leu Ser Pro Gly Ala	1191
75 80 85 90	
AAG CAG AAC ATC CAA CTG ATC AAC ACC AAC GGC AGT TGG CAC ATC AAT Lys Gln Asn Ile Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn	1239
95 100 105	
AGC ACG GCC TTG AAC TGC AAT GAA AGC CTT AAC ACC GGC TGG TTA GCA Ser Thr Ala Leu Asn Cys Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala	1287
110 115 120	
GGG CTC TTC TAT CAC CAC AAA TTC AAC TCT TCA GGT TGT CCT GAG AGG Gly Leu Phe Tyr His His Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg	1335
125 130 135	
TTG GCC AGC TGC CGA CGC CTT ACC GAT TTT GCC CAG GGC GGG GGT CCT Leu Ala Ser Cys Arg Arg Leu Thr Asp Phe Ala Gln Gly Gly Pro	1383
140 145 150	
ATC AGT TAC GCC AAC GGA AGC GGC CTC GAT GAA CGC CCC TAC TGC TGG Ile Ser Tyr Ala Asn Gly Ser Gly Leu Asp Glu Arg Pro Tyr Cys Trp	1431
155 160 165 170	
CAC TAC CCT CCA AGA CCT TGT GGC ATT GTG CCC GCA AAG AGC GTG TGT	1479

His Tyr Pro Pro Arg Pro Cys Gly Ile Val Pro Ala Lys Ser Val Cys			
175	180	185	
GGC CCG GTA TAT TGC TTC ACT CCC AGC CCC GTG GTG GTG GGA ACG ACC			1527
Gly Pro Val Tyr Cys Phe Thr Pro Ser Pro Val Val Val Gly Thr Thr			
190	195	200	
GAC AGG TCG GGC GCG CCT ACC TAC AGC TGG GGT GCA AAT GAT ACG GAT			1575
Asp Arg Ser Gly Ala Pro Thr Tyr Ser Trp Gly Ala Asn Asp Thr Asp			
205	210	215	
GTC TTT GTC CTT AAC AAC ACC AGG CCA CCG CTG GGC AAT TGG TTC GGT			1623
Val Phe Val Leu Asn Asn Thr Arg Pro Pro Leu Gly Asn Trp Phe Gly			
220	225	230	
TGC ACC TGG ATG AAC TCA ACT GGA TTC ACC AAA GTG TGC GGA GCG CCC			1671
Cys Thr Trp Met Asn Ser Thr Gly Phe Thr Lys Val Cys Gly Ala Pro			
235	240	245	250
CCT TGT GTC ATC GGA GGG GTG GGC AAC AAC ACC TTG CTC TGC CCC ACT			1719
Pro Cys Val Ile Gly Gly Val Gly Asn Asn Thr Leu Leu Cys Pro Thr			
255	260	265	
GAT TGC TTC CGC AAG CAT CCG GAA GCC ACA TAC TCT CCG TGC GGC TCC			1767
Asp Cys Phe Arg Lys His Pro Glu Ala Thr Tyr Ser Arg Cys Gly Ser			
270	275	280	
GGT CCC TGG ATT ACA CCC AGG TGC ATG GTC GAC TAC CCG TAT AGG CTT			1815
Gly Pro Trp Ile Thr Pro Arg Cys Met Val Asp Tyr Pro Tyr Arg Leu			
285	290	295	
TGG CAC TAT CCT TGT ACC ATC AAT TAC ACC ATA TTC AAA GTC AGG ATG			1863
Trp His Tyr Pro Cys Thr Ile Asn Tyr Thr Ile Phe Lys Val Arg Met			
300	305	310	
TAC GTG GGA GGG GTC GAG CAC AGG CTG GAA GCG GCC TGC AAC TGG ACG			1911
Tyr Val Gly Gly Val Glu His Arg Leu Glu Ala Ala Cys Asn Trp Thr			
315	320	325	330
CGG GGC GAA CGC TGT GAT CTG GAA GAC AGG GAC AGG TCC GAG CTC AGC			1959
Arg Gly Glu Arg Cys Asp Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser			
335	340	345	
CCG TTA CTG CTG TCC ACC ACG CAG TGG CAG GTC CTT CCG TGT TCT TTC			2007
Pro Leu Leu Leu Ser Thr Thr Gln Trp Gln Val Leu Pro Cys Ser Phe			
350	355	360	
ACG ACC CTG CCA GCC TAGATCTCTG AAGTGAAGAT GGATGCAGAA TTCCGACATG			2062
Thr Thr Leu Pro Ala			
365			
ACTCAGGATA TGAAGTTCAT CATCAAAAAT TGGTGTCTT TGCAGAAGAT GTGGGTCAA			2122
ACAAAGGTGC AATCATTGGA CTCATGGTGG GCGGTGTGT CATAGCGACA GTGATCGTCA			2182

TCACCTTGGT GATGCTGAAG AAGAAACAGT ACACATCCAT TCATCATGGT GTGGTGGAGG	2242
TTGACGCCGC TGTCACCCCA GAGGAGCGCC ACCTGTCCAA GATGCAGCAG AACGGCTACG	2302
AAAATCCAAC CTACAAGTTC TTTGAGCAGA TGCAGAACTA GACCCCCGCC ACAGCAGCCT	2362
CTGAAGTTGG ACAGCAAAAC CATTGCTTCA CTACCCATCG GTGTCCATT ATAGAATAAT	2422
GTGGGAAGAA ACAAAACCGT TTTATGATT ACTCATTATC GCCTTTGAC AGCTGTGCTG	2482
TAACACAAAGT AGATGCCCTGA ACTTGAATTA ATCCACACAT CAGTAATGTA TTCTATCTCT	2542
CTTTACATTG TGGTCTCTAT ACTACATTAT TAATGGTTT TGTGTACTGT AAAGAATTAA	2602
GCTGTATCAA ACTAGTGCAT GAATAGGCCG CTCGAGCATG CATCTAGAGG GCCCTATTCT	2662
ATAGTGTAC CCAAATGCTC GCTGATCAGC CTCGACTGTG CCTTCTAGTT GCCAGCCATC	2722
TGTGTGTTGC CCCTCCCCCG TGCCCTCCTT GACCCCTGGAA GGTGCCACTC CCACTGTCC	2782
TTCCTAATAA AATGAGGAAA TTGCATCGCA TTGTCTGAGT AGGTGTCAATT CTATTCTGGG	2842
GGGTGGGTG GGGCAGGACA GCAAGGGGAA GGATTGGGAA GACAATAGCA GGCATGCTGG	2902
GGATGCGGTG GGCTCTATGG AACCAGCTGG GGCTCGAGGG GGGATCCCCA CGCGCCCTGT	2962
AGCGGCGCAT TAAGCGCGC CGGTGTGGTG GTTACCGCGA GCGTGACCGC TACACTTGCC	3022
AGCGCCCTAG CGCCCGCTCC TTTCGCTTTT TTCCCTTCCT TTCTCGCCAC GTTCGCCGGC	3082
TTTCCCCGTC AAGCTCTAAA TCGGGGCATC CCTTTAGGGT TCCGATTTAG TGCTTTACGG	3142
CACCTCGACC CCAAAAAACT TGATTAGGGT GATGGTTAC GTAGTGGGCC ATCGCCCTGA	3202
TAGACGGTTT TTGCTCTTTA CTGAGCACTC TTTAATAGTG GACTCTTGTT CCAAACGTGA	3262
ACAACACTCA ACCCTATCTC GGTCTATTCT TTTGATTAT AAGATTCCA TCGCCATGTA	3322
AAAGTGTAC AATTAGCATT AAATTACTTC TTTATATGCT ACTATTCTTT TGGCTTCGTT	3382
CACGGGGTGG GTACCGAGCT CGAATTCTGT GGAATGTGTG TCAGTTAGGG TGTGGAAAGT	3442
CCCCAGGCTC CCCAGGCAGG CAGAAAGTATG CAAAGCATGC ATCTCAATTAA GTCAGCAACC	3502
AGGTGTGGAA AGTCCCCAGG CTCCCCAGCA GGCAGAAAGTA TGCAAAGCAT GCATCTCAAT	3562
TAGTCAGCAA CCATAGTCCC GCCCCTAAC CCGCCCATCC CGCCCCTAAC TCCGCCAGT	3622
TCCGCCATT CTCCGCCCA TGGCTGACTA ATTTTTTTTA TTTATGCAGA GGCCGAGGCC	3682
GCCTCGGCCT CTGAGCTATT CCAGAAAGTAG TGAGGAGGCT TTTTTGGAGG CCTAGGCTTT	3742
TGCAAAAAGC TCCCAGGAGC TTGGATATCC ATTTTCGGAT CTGATCAAGA GACAGGATGA	3802
GGATCGTTTC GCATGATTGA ACAAGATGGA TTGCACGCCAG GTTCTCCGGC CGCTTGGGTG	3862

GAGAGGCTAT TCGGCTATGA CTGGCACAA CAGACAATCG GCTGCTCTGA TGCCGCCGTG	3922
TTCCGGCTGT CAGCGCAGGG GCGCCCGGTT CTTTTTGTCAGACCGACCT GTCCGGTGCC	3982
CTGAATGAAC TGCAGGACGA GGCAGCGCGG CTATCGTGGC TGGCCACGAC GGGCGTTCCCT	4042
TGCGCAGCTG TGCTCGACGT TGTCACTGAA GCGGGAAAGGG ACTGGCTGCT ATTGGCGAA	4102
GTGCCGGGGC AGGATCTCCT GTCATCTCAC CTTGCTCCTG CCGAGAAAGT ATCCATCATG	4162
GCTGATGCAA TCGGGCGGCT GCATACGCTT GATCCGGCTA CCTGCCATT CGACCACCAA	4222
GCGAAACATC GCATCGAGCG AGCACGTACT CGGATGGAAG CCGGTCTTGT CGATCAGGAT	4282
GATCTGGACG AAGAGCATCA GGGGCTCGCG CCAGCCGAAC TGTCGCCAG GCTCAAGGCG	4342
CGCATGCCCG ACGGCGAGGA TCTCGTCGTG ACCCATGGCG ATGCCCTGCTT CCCGAATATC	4402
ATGGTGGAAA ATGGCCGCTT TTCTGGATTC ATCGACTGTG GCCGGCTGGG TGTGGCGGAC	4462
CGCTATCAGG ACATAGCGTT GGCTACCCGT GATATTGCTG AAGAGCTTGG CGCGAATGG	4522
GCTGACCGCT TCCTCGTGCT TTACGGTATC GCGCTCCCG ATTGCAAGCG CATGCCCTTC	4582
TATCGCCTTC TTGACGAGTT CTTCTGAGCG GGACTCTGGG GTTCGAAATG ACCGACCAAG	4642
CGACGCCAA CCTGCCATCA CGAGATTCG ATTCCACCCCG CGCCTTCTAT GAAAGGTTGG	4702
GCTTCGGAAT CGTTTCCGG GACGCCGGCT GGATGATCCT CCAGCGCGGG GATCTCATGC	4762
TGGAGTTCTT CGCCCACCCC AACTTGTAA TTGCAGCTTA TAATGGTTAC AAATAAAGCA	4822
ATAGCATCAC AAATTCACA AATAAAGCAT TTTTTCACT GCATTCTAGT TGTGGTTTGT	4882
CCAAACTCAT CAATGTATCT TATCATGTCT GGATCCCGTC GACCTCGAGA GCTTGGCGTA	4942
ATCATGGTCA TAGCTGTTTC CTGTGTGAAA TTGTTATCCG CTCACAATTCA CACACAACAT	5002
ACGAGCCGGA ACCATAAAAGT GTAAAGCCTG GGGTGCCTAA TGAGTGAGCT AACTCACATT	5062
AATTGCGTTG CGCTCACTGC CCGCTTCCA GTCGGGAAAC CTGTCGTGCC AGCTGCATTA	5122
ATGAATCGGC CAAAGCGCGG GGAGAGCCGG TTTGCGTATT GGGCGCTCTT CGCCTTCTC	5182
GCTCACTGAC TCGCTCGCGCT CGGTCCGTTCG GCTGCGGCCGA GCGGTATCAG CTCACTCAAA	5242
GGCGGTATAA CGGTTATCCA CAGAACAGG GGATAACGCA GGAAAGAACAA TGTGAGCAAA	5302
AGGCCAGCAA AAGGCCAGGA ACCGTAAAAA GGCGCGTTG CTGGCGTTT TCCATAGGCT	5362
CCGCCCCCT GACGGACATC ACAAAAATCG ACGCTCAAGT CAGAGGTGGC GAAACCCGAC	5422
AGGACTATAA AGATACCAGG CGTTTCCCCC TGGAAGCTCC CTCGTGCGCT CTCCTGTTCC	5482

GACCCTGCCG CTTACCGGAT ACCTGTCCGC CTTCTCCCT TCGGGAAGCG TGGCGCTTC	5542
TCAATGCTCA CGCTGTAGGT ATCTCAGTTC GGTGTAGGTC GTTCGCTCCA AGCTGGGCTG	5602
TGTGCACGAA CCCCCCGTTC AGCCCGACCG CTGCGCCTTA TCCGGTAACT ATCGTCTTGA	5662
GTCCAACCCG GTAAGACACCG ACTTATCGCC ACTGGCAGCA GCCACTGGTA ACAGGATTAG	5722
CAGAGCGAGG TATGTAGGCG GTGCTACAGA GTTCTGAAG TGGTGGCCTA ACTACGGCTA	5782
CACTAGAAGG ACAGTATTTG GTATCTGCGC TCTGCTGAAG CCAGTTACCT TCGGAAAAAG	5842
AGTTGGTAGC TCTTGATCCG GCAAACAAAC CACCGCTGGT AGCGGTGGTT TTTTTGTTG	5902
CAAGCAGCAG ATTACCGCGA GAAAAAAAGG ATCTCAAGAA GATCCTTGA TCTTTCTAC	5962
GGGGTCTGAC GCTCAGTGGA ACGAAAATC ACGTTAAGGG ATTTTGGTCA TGAGATTATC	6022
AAAAAGGATC TTCACCTAGA TCCTTTAAA TTAAAAATGA AGTTTAAAT CAATCTAAAG	6082
TATATATGAG TAAACTGGT CTGACAGTTA CCAATGCTTA ATCAGTGAGG CACCTATCTC	6142
AGCGATCTGT CTATTCGTT CATCCATAGT TGCCTGACTC CCCGTCGTGT AGATAACTAC	6202
GATACGGGAG GGCTTACCAT CTGGCCCCAG TGCTGCAATG ATACCGCGAG ACCCACGCTC	6262
ACCGGCTCCA GATTATTCAG CAATAAACCA GCCAGCCGGA AGGGCCGAGC GCAGAAGTGG	6322
TCCTGCAACT TTATCCGCCT CCATCCAGTC TATTAATTGT TGCCGGGAAG CTAGAGTAAG	6382
TAGTTGCCA GTTAATAGTT TGCACACGT TGTGCCCCATT GCTACAGGCA TCGTGGTGTC	6442
ACGCTCGTCG TTTGGTATGG CTTCAATTCAAG CTCCGGTTCC CAACGATCAA GGCGAGTTAC	6502
ATGATCCCCC ATGTTGTGCA AAAAAGCGGT TAGCTCCTTC GGTCTCCGA TCGTTGTCAG	6562
AAGTAAGTTG GCCCGAGTGT TATCACTCAT GTTATGGCA GCACTGCATA ATTCTCTTAC	6622
TGTCATGCCA TCCGTAAGAT GCTTTCTGT GACTGGTGAG TACTCAACCA AGTCATTCTG	6682
AGAATAGTGT ATGCGGCGAC CGAGTTGCTC TTGCCCCGG TCAATACGGG ATAATACCGC	6742
GCCACATAGC AGAACTTTAA AAGTGCTCAT CATTGGAAAA CGTTCTTCGG GGCGAAAATC	6802
CTCAAGGATC TTACCGCTGT TGAGATCCAG TTGATGTAA CCCACTCGTG CACCCAACTG	6862
ATCTTCAGCA TCTTTTACTT TCACCAGCGT TTCTGGGTGA GCAAAACAG GAAGGAAAAA	6922
TGCCGAAAA AAGGGAATAA GGGCGACACG GAAATGTTGA ATACTCATAAC TCTTCCTTTT	6982
TCAATATTAT TGAAGCATTG ATCAGGGTTA TTGTGTCTAG AGCGGATACA TATTTGAATG	7042
TATTTAGAAA AATAAACAAA TAGGGGTTCC GCGCACATTG CCCCCAAAAG TGCCACCTGA	7102
CGTC	7106

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 367 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Leu Pro Gly Leu Ala Leu Leu Leu Ala Ala Ala Trp Thr Ala Arg
1 5 10 15

Ala Leu Glu Val Pro Thr Asp Gly Asn Ala Gly Leu Leu Ala Glu Pro
20 25 30

Gln Ile Ala Met Phe Cys Gly Arg Leu Asn Met His Met Asn Val Gln
35 40 45

Asn Gly Lys Trp Asp Ser Asp Pro Ser Gly Thr Lys Thr Cys Ile Asp
50 55 60

Thr Lys Glu Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala
65 70 75 80

Gly Leu Val Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu
85 90 95

Ile Asn Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys
100 105 110

Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His
115 120 125

Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg
130 135 140

Leu Thr Asp Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly
145 150 155 160

Ser Gly Leu Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Pro
165 170 175

Cys Gly Ile Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe
180 185 190

Thr Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro
195 200 205

Thr Tyr Ser Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu Asn Asn
210 215 220

Thr Arg Pro Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser
 225 230 235 240

Thr Gly Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly
 245 250 255

Val Gly Asn Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys His
 260 265 270

Pro Glu Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro
 275 280 285

Arg Cys Met Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr
 290 295 300

Ile Asn Tyr Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu
 305 310 315 320

His Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp
 325 330 335

Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Ser Thr
 340 345 350

Thr Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala
 355 360 365

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4810 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 2227..2910

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GCGTAATCTG CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTGCGCCGG	60
ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG CAGATACCAA	120
ATACTGTCCT TCTAGTGTAG CCGTAGTTAG GCCACCCTT CAAGAACTCT GTAGCACCGC	180
CTACATACCT CGCTCTGCTA ATCCTGTTAC CAGTGGCTGC TGCCAGTGGC GATAAGTCGT	240
GTCTTACCGG GTTGGACTCA AGACGATAGT TACCGGATAA GGCGCAGCGG TCGGGCTGAA	300

CGGGGGGTTTC	GTGCACACAG	CCCAGCTTGG	AGCGAACGAC	CTACACCGAA	CTGAGATACC	360
TACAGCGTGA	GCATTGAGAA	AGGCCACGC	TTCCCGAAGG	GAGAAAGGCG	GACAGGTATC	420
CGGTAAGCGG	CAGGGTCGGA	ACAGGAGAGC	GCACGAGGG	GCTTCCAGGG	GGAAACGCCT	480
GGTATCTTTA	TAGTCCTGTC	GGGTTTCGCC	ACCTCTGACT	TGAGCGTCGA	TTTTTGTGAT	540
GCTCGTCAGG	GGGGCGGAGC	CTATGGAAAA	ACGCCAGCAA	CGCAAGCTAG	CTTCTAGCTA	600
GAAATTGTAA	ACGTTAATAT	TTTGTAAAAA	TCGCCTTAA	ATTTTTGTTA	AATCAGCTCA	660
TTTTTTAACC	AATAGGCCGA	AATCGGAAA	ATCCCTTATA	AATCAAAAGA	ATAGCCCGAG	720
ATAGGGTTGA	GTGTTGTC	AGTTTGGAAC	AAGAGTCCAC	TATTAAGAA	CGTGGACTCC	780
AACGTCAAAG	GGCGAAAAAC	CGTCTATCAG	GGCGATGGCC	GCCCACTAGC	TGAACCATCA	840
CCCAAATCAA	GTTTTTGGG	GTGAGGTGC	CGTAAAGCAC	TAAATCGGAA	CCCTAAAGGG	900
AGCCCCCGAT	TTAGAGCTTG	ACGGGGAAAG	CCGGCGAACG	TGGCGAGAAA	GGAAGGGAAG	960
AAAGCGAAAG	GAGCGGGCGC	TAGGGCGCTG	GCAAGTGTAG	CGGTACGCT	GGCGTAACC	1020
ACCACACCCG	CCCGCGTTAA	TGCGCCGCTA	CAGGGCGCGT	ACTATGGTTG	CTTGACGAG	1080
ACCGTATAAC	GTGCTTCCT	CGTIGGAATC	AGAGCGGGAG	CTAAACAGGA	GGCGATTAA	1140
AGGGATTTA	GACAGGAACG	GTACGCCAGC	TGGATCACCG	CGGTCTTCT	CAACGTAACA	1200
CTTTACAGCG	GGCGTCATT	TGATATGATG	CGCCCCGCTT	CCCGATAAGG	GAGCAGGCCA	1260
GTAAAAGCAT	TACCCGTGGT	GGGGTTCCCG	AGCGGCCAAA	GGGAGCAGAC	TCTAAATCTG	1320
CCGTCATCGA	CTTCGAAGGT	TCGAATCCTT	CCCCCACCAC	CATCACTTTC	AAAAGTCCGA	1380
AAGAATCTGC	TCCCTGCTTG	TGTGTTGGAG	GTGCGTGAGT	AGTGGCGAG	TAAAATTAA	1440
GCTACAACAA	GGCAAGGCTT	GACCGACAAT	TGCATGAAGA	ATCTGCTTAG	GGTTAGGCGT	1500
TTTGCCTGTC	TTCGCGATGT	ACGGGCCAGA	TATACCGTT	GACATTGATT	ATTGACTAGT	1560
TATTAATAGT	AATCAATTAC	GGGGTCATTA	GTTCATAGCC	CATATATGGA	GTTCGGCGTT	1620
ACATAACTTA	CGGTAAATGG	CCCGCCTGGC	TGACCGCCCA	ACGACCCCCG	CCCATTGACG	1680
TCAATAATGA	CGTATGTTCC	CATAGTAACG	CCAATAGGGA	CTTTCCATTG	ACGTCAATGG	1740
GTGGACTATT	TACGGTAAAC	TGCCCACTTG	GCAGTACATC	AAGTGTATCA	TATGCCAAGT	1800
ACGCCCCCTA	TTGACGTCAA	TGACGGTAAA	TGGCCCGCCT	GGCATTATGC	CCAGTACATG	1860
ACCTTATGGG	ACTTTCTAC	TTGGCAGTAC	ATCTACGTAT	TAGTCATCGC	TATTACCATG	1920
GTGATGCGGT	TTTGGCAGTA	CATCAATGGG	CGTGGATAGC	GGTTTGACTC	ACGGGGATTT	1980

CCAAGTCTCC ACCCCATTGA CGTCAATGGG AGTTTGTGTTT GGCACCAAAA TCAACGGGAC	2040
TTTCCAAAT GTCGTAACAA CTCCGCCCA TTGACGAAA TGGCGGTAG GCGTGTACGG	2100
TGGGAGGTCT ATATAAGCAG AGCTCTCTGG CTAACTAGAG AACCCACTGC TTAACTGGCT	2160
TATCGAAATT AATACGACTC ACTATAGGA GACCGGAAGC TTGGTACCGA GCTCGGATCT	2220
GCCACC ATG GCA ACA GGA TCA AGA ACA TCA CTG CTG CTG GCA TTT GGA Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly	2268
1 5 10	
CTG CTG TGT CTG CCA TGG CTG CAA GAA GGA TCA GCA GCA GCA GCG Leu Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Ala Ala Ala 15 20 25 30	2316
AAT TCG GAT CCC TAC CAA GTG CGC AAT TCC TCG GGG CTT TAC CAT GTC Asn Ser Asp Pro Tyr Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val 35 40 45	2364
ACC AAT GAT TGC CCT AAT TCG AGT ATT GTG TAC GAG GCG GCC GAT GCC Thr Asn Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Ala Asp Ala 50 55 60	2412
ATC CTA CAC ACT CCG GGG TGT GTC CCT TGC GTT CGC GAG GGT AAC GCC Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn Ala 65 70 75	2460
TCG AGG TGT TGG GTG GCG GTG ACC CCC ACG GTG GCC ACC AGG GAC GGC Ser Arg Cys Trp Val Ala Val Thr Pro Thr Val Ala Thr Arg Asp Gly 80 85 90	2508
AAA CTC CCC ACA ACG CAG CTT CGA CGT CAT ATC GAT CTG CTC GTC GGG Lys Leu Pro Thr Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly 95 100 105 110	2556
AGC GCC ACC CTC TGC TCG GCC CTC TAC GTG GGG GAC CTG TGC GGG TCT Ser Ala Thr Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser 115 120 125	2604
GTC TTT CTT GTT GGT CAA CTG TTT ACC TTC TCT CCC AGG CGC CAC TGG Val Phe Leu Val Gly Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp 130 135 140	2652
ACG ACG CAA GAC TGC AAT TGT TCT ATC TAT CCC GGT CAT ATA ACG GGT Thr Thr Gln Asp Cys Asn Cys Ser Ile Tyr Pro G. His Ile Thr Gly 145 150 155	2700
CAT CGT ATG GCA TGG GAT ATG ATG AAC TGG TCC CCT ACG GCA GCG His Arg Met Ala Trp Asp Met Met Asn Trp Ser Pro Thr Ala Ala 160 165 170	2748
TTG GTG GTA GCT CAG CTG CTC CGG ATC CCA CAA GCC ATC TTG GAC ATG Leu Val Val Ala Gln Leu Leu Arg Ile Pro Gln Ala Ile Leu Asp Met	2796

175	180	185	190	
ATC GCT GGT GCC CAC TCG GGA GTC CTG GCG GGC ATA GCG TAT TTC TCC Ile Ala Gly Ala His Trp Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser				2844
195	200		205	
ATG GTG GGG AAC TGG GCG AAG GTC CTG GTA GTG CTG CTG CTA TTT GCC Met Val Gly Asn Trp Ala Lys Val Leu Val Leu Leu Leu Phe Ala	210	215	220	2892
GGC GTT GAC GCG GAG ATC TAATCTAGAG GGCCCTATTC TATAGTGTCA Gly Val Asp Ala Glu Ile				2940
225				
CCTAAATGCT AGAGGATCTT TGTGAAGGAA CCTTACTCT GTGGTGTGAC ATAATTGGAC				3000
AAACTACCTA CAGAGATTAA AAGCTCTAAG GTAAATATAA AATTTTAAG TGTATAATGT				3060
GTTAAACTAC TGATTCTAAT TGTTTGTGTA TTTTAGATTTC CAACCTATGG AACTGATGAA				3120
TGGGAGCAGT GGTGGAATGC CTTTAATGAG GAAAACCTGT TTTGCTCAGA AGAAATGCCA				3180
TCTAGTGATG ATGAGGCTAC TGCTGACTCT CAACATTCTA CTCCCTCCAAA AAAGAAGAGA				3240
AAGGTAGAAG ACCCCAAGGA CTTTCCCTCA GAATTGCTAA GTTTTTGAG TCATGCTGTG				3300
TTTAGTAATA GAACTCTTGC TTGCTTGCT ATTTACACCA CAAAGGAAAA AGCTGCACTG				3360
CTATACAAGA AAATTATGGA AAAATATTCT GTAACCTTTA TAAGTAGGCA TAACAGTTAT				3420
AATCATAACA TACTGTTTT TCTTACTCCA CACAGGCATA GAGTGTCTGC TATTAATAAC				3480
TATGCTCAA AATTGTGTAC CTTTAGCTTT TTAATTGTA AAGGGGTTAA TAAGGAATAT				3540
TTGATGTATA GTGCCTTGAC TAGAGATCAT AATCAGCCAT ACCACATTG TAGAGGTTTT				3600
ACTTGCTTTA AAAAACCTCC CACACCTCCC CCTGAACCTG AAACATAAAA TGAATGCAAT				3660
TGTTGTTGTT AACTTGTAA TTGCAGCTTA TAATGGTAC AAATAAAGCA ATAGCATCAC				3720
AAATTTCACA AATAAAACCAT TTTTTCACT GCATTCTAGT TGTGGTTTGT CCAAACTCAT				3780
CAATGTATCT TATCATGTCT GGATCGATCC CGCCATGGTA TCAACGCCAT ATTTCTATT				3840
ACAGTAGGGA CCTCTTCGTT GTGTAGGTAC CGCTGTATTG CTAGGGAAAT AGTAGAGGCA				3900
CCTTGAAC TG TCTGCATCAG CCATATAGCC CCCGCTGTT GACTTACAAA CACAGGCACA				3960
GTACTGACAA ACCCATACAC CTCCTCTGAA ATACCCATAG TTGCTAGGGC TGTCTCCGAA				4020
CTCATTACAC CCTCCAAAGT CAGAGCTGTA ATTTGCCAT CAAGGGCAGC GAGGGCTTCT				4080
CCAGATAAAA TAGCTTCTGC CGAGAGTCCC GTAAGGGTAG ACACCTCAGC TAATCCCTCG				4140
ATGAGGTCTA CTAGAATAGT CAGTGCAGCT CCCATTGAA AAATTCACTT ACTTGATCAG				4200

CTTCAGAAGA TGGCGGAGGG CCTCCAACAC AGTAATTTC CTCCGACTC TTAAAATAGA	4260
AAATGTCAAG TCAGTTAACG AGGAAGTGGG CTAACTGACG CAGCTGGCCG TGCGACATCC	4320
TCTTTAATT AGTTGCTAGG CAACGCCCTC CAGAGGGCGT GTGGTTTGC AAGAGGAAGC	4380
AAAAGCCTCT CCACCCAGGC CTAGAATGTT TCCACCCAAT CATTACTATG ACAACAGCTG	4440
TTTTTTTTAG TATTAAGCAG AGGCCGGGA CCCCTGGCCC GCTTACTCTG GAGAAAAAGA	4500
AGAGAGGCAT TGTAGAGGCT TCCAGAGGCA ACTTGTAAA ACAGGACTGC TTCTATTCT	4560
GTCACACTGT CTGGCCCTGT CACAAGGTCC AGCACCTCCA TACCCCTTT AATAAGCAGT	4620
TTGGGAACGG GTGCGGGTCT TACTCCGCC ATCCCGCCCC TAACTCCGCC CAGTTCCGCC	4680
CATTCTCCGC CCCATGGCTG ACTAATTCTT TTTATTTATG CAGAGGCCGA GGCCGCCTCG	4740
GCCTCTGAGC TATTCCAGAA GTAGTGAGGA GGCTTTTTG GAGGCCTAGG CTTTGCAAA	4800
AAGCTAATTC	4810

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 228 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu			
1	5	10	15
Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Ala Ala Ala Asn Ser			
20	25	30	
Asp Pro Tyr Gln Val Arg Asn Ser Ser Gly Leu Tyr His Val Thr Asn			
35	40	45	
Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala Ala Asp Ala Ile Leu			
50	55	60	
His Thr Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn Ala Ser Arg			
65	70	75	80
Cys Trp Val Ala Val Thr Pro Thr Val Ala Thr Arg Asp Gly Lys Leu			
85	90	95	
Pro Thr Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser Ala			
100	105	110	

Thr Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Phe
 115 120 125

Leu Val Gly Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr
 130 135 140

Gln Asp Cys Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His Arg
 145 150 155 160

Met Ala Trp Asp Met Met Asn Trp Ser Pro Thr Ala Ala Leu Val
 165 170 175

Val Ala Gln Leu Leu Arg Ile Pro Gln Ala Ile Leu Asp Met Ile Ala
 180 185 190

Gly Ala His Trp Gly Val Leu Ala Gly Ile Ala Tyr Phe Ser Met Val
 195 200 205

Gly Asn Trp Ala Lys Val Leu Val Val Leu Leu Phe Ala Gly Val
 210 215 220

Asp Ala Glu Ile
 225

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5323 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 2227..3423

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGCTAATCTG CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTTTGCCGG	60
ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG CAGATACCAA	120
ATACTGTCTT TCTAGTGTAG CCGTAGTTAG GCCACCCTT CAAGAACTCT GTAGCACCAC	180
CTACATACCT CGCTCTGCTA ATCCTGTTAC CAGTGGCTGC TGCCAGTGGC GATAAGTCGT	240
GTCTTACCGG GTTGGACTCA AGACGATAGT TACCGGATAA GGCGCAGCGG TCGGGCTGAA	300
CGGGGGGTTTC GTGCACACAG CCCAGCTTGG AGCGAACGAC CTACACCGAA CTGAGATACC	360

TACAGCGTGA	GCATTGAGAA	AGGCCACGC	TTCCCGAAGG	GAGAAAGGCG	GACAGGTATC	420
CGGTAAGCGG	CAGGGTCGGA	ACAGGAGAGC	GCACGAGGGA	GCTTCCAGGG	GGAAACGCCT	480
GGTATCTTA	TAGTCCTGTC	GGGTTTCGCC	ACCTCTGACT	TGAGCGTCGA	TTTTTGTGAT	540
GCTCGTCAGG	GGGGCGGAGC	CTATGGAAAA	ACGCCAGCAA	CGCAAGCTAG	CTTCTAGCTA	600
GAAATTGTAA	ACGTTAATAT	TTTGTAAAAA	TTCGCGTTAA	ATTTTGTAA	AATCAGCTCA	660
TTTTTTAAC	AATAGGCCGA	AATCGGAAA	ATCCCTTATA	AATCAAAAGA	ATAGCCCGAG	720
ATAGGGTTGA	GTGTTGTTCC	AGTTTGGAAC	AAGAGTCCAC	TATTAAGAA	CGTGGACTCC	780
AACGTCAAAG	GGCGAAAAAC	CGTCTATCAG	GGCGATGCC	GCCCACTAGC	TGAACCATCA	840
CCCAAATCAA	GTTTTTGGG	GTCGAGGTGC	CGTAAAGCAC	TAAATCGAA	CCCTAAAGGG	900
AGCCCCCGAT	TTAGAGCTTG	ACGGGGAAAG	CCGGCGAACG	TGGCGAGAAA	GGAAAGGGAAG	960
AAAGCGAAAG	GAGCGGGCGC	TAGGGCGCTG	GCAAGTGTAG	CGGTACGCT	GCGCGTAACC	1020
ACCACACCCG	CCGGCGTTAA	TGCGCCGCTA	CAGGGCGCGT	ACTATGGTIG	CTTIGACGAG	1080
ACCGTATAAC	GTGCTTCCCT	CGTTGGAATC	AGAGCGGGAG	CTAAACAGGA	GGCGATTAA	1140
AGGGATTTA	GACAGGAACG	GTACGCCAGC	TGGATCACCG	CGGTCTTCT	CAACGTAACA	1200
CTTTACAGCG	GCGCGTCATT	TGATATGATG	CGCCCCGCTT	CCCGATAAGG	GAGCAGGCCA	1260
GTAAAAGCAT	TACCCGTGGT	GGGGTTCCCG	AGCGGCCAAA	GGGAGCAGAC	TCTAAATCTG	1320
CCGTCATCGA	CTTCGAAGGT	TCGAATCCTT	CCCCACCCAC	CATCACTTTC	AAAAGTCCGA	1380
AAGAATCTGC	TCCCTGCTTG	TGTGTTGGAG	GTCGCTGAGT	AGTGCAGCAG	AAAATTAA	1440
GCTACAACAA	GGCAAGGCTT	GACCGACAAT	TGCATGAAGA	ATCTCCTTAG	GGTTAGGCGT	1500
TTTGCCTGC	TTCGCGATGT	ACGGGCCAGA	TATACCGCTT	GACATTGATT	ATTGACTAGT	1560
TATTAATAGT	AATCAATTAC	GGGGTCATTA	GTTCATAGCC	CATATATGGA	GTTCCCGCGTT	1620
ACATAACTTA	CGGTAAATGG	CCCGCCTGGC	TGACCGCCCA	ACGACCCCCG	CCCATTGACG	1680
TCAATAATGA	CGTATGTTCC	CATAGTAACG	CCAATAGGGA	CTTCCATTG	ACGTCAATGG	1740
GTGGACTATT	TACGGTAAAC	TGCCCACTTG	GCAGTACATC	AAGTGTATCA	TATGCCAAGT	1800
ACGCCCCCTA	TTGACGTCAA	TGACGGTAAA	TGGCCCGCCT	GGCATTATGC	CCAGTACATG	1860
ACCTTATGGG	ACTTTCCTAC	TTGGCAGTAC	ATCTACGTAT	TAGTCATCGC	TATTACCATG	1920
GTGATGCCGT	TTTGGCAGTA	CATCAATGGG	CGTGGATAGC	GGTTGACTC	ACGGGGATTT	1980
CCAAGTCTCC	ACCCCATGTA	CGTCAATGGG	AGTTTGTGTTT	GGCACCAAAA	TCAACGGGAC	2040

TTTCCAAAAT GTCGTAACAA CTCCGCCCCA TTGACGCAAA TGGGCGGTAG GCGTGTACGG	2100
TGGGAGGTCT ATATAGCAG AGCTCTCTGG CTAACTAGAG AACCCACTGC TAACTGGCT	2160
TATCGAAATT AATACGACTC ACTATAGGGA GACCGGAAGC TTGGTACCGA GCTCGGATCT	2220
GCCACC ATG GCA ACA GGA TCA AGA ACA TCA CTG CTG CTG GCA TTT GGA	2268
Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly	
1 5 10	
CTG CTG TGT CTG CCA TGG CTG CAA GAA GGA TCA GCA GCA GCA GCG	2316
Leu Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Ala Ala Ala Ala	
15 20 25 30	
AAT TCA GAA ACC CAC GTC ACC GGG GGA AGT GCC GGC CAC ACC ACG GCT	2364
Asn Ser Glu Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala	
35 40 45	
GGG CTT GTT CGT CTC CTT TCA CCA GGC GCC AAG CAG AAC ATC CAA CTG	2412
Gly Leu Val Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu	
50 55 60	
ATC AAC ACC AAC GGC AGT TGG CAC ATC AAT AGC ACG GCC TTG AAC TGC	2460
Ile Asn Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys	
65 70 75	
AAT GAA AGC CTT AAC ACC GGC TGG TTA GCA GGG CTC TTC TAT CAC CAC	2508
Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His	
80 85 90	
AAA TTC AAC TCT TCA GGT TGT CCT GAG AGG TTG GCC AGC TGC CGA CGC	2556
Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg	
95 100 105 110	
CTT ACC GAT TTT GCC CAG GGC GGG GGT CCT ATC AGT TAC GCC AAC GGA	2604
Leu Thr Asp Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly	
115 120 125	
AGC GGC CTC GAT GAA CGC CCC TAC TGC TGG CAC TAC CCT CCA AGA CCT	2652
Ser Gly Leu Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Pro	
130 135 140	
TGT GGC ATT GTG CCC GCA AAG AGC GTG TGT GGC CCG GTA TAT TGC TTC	2700
Cys Gly Ile Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe	
145 150 155	
ACT CCC AGC CCC GTG GTG GTG GGA ACG ACC GAC AGG TCG GGC GCG CCT	2748
Thr Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro	
160 165 170	
ACC TAC AGC TGG GGT GCA AAT GAT ACG GAT GTC TTT GTC CTT AAC AAC	2796
Thr Tyr Ser Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu Asn Asn	
175 180 185 190	

ACC AGG CCA CCG CTG GGC AAT TGG TTC GGT TGC ACC TGG ATG AAC TCA Thr Arg Pro Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser 195 200 205	2844
ACT GGA TTC ACC AAA GTG TGC CGA GCG CCC CCT TGT GTC ATC GGA GGG Thr Gly Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly 210 215 220	2892
GTG GGC AAC AAC ACC TTG CTC TGC CCC ACT GAT TGC TTC CGC AAG CAT Val Gly Asn Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys His 225 230 235	2940
CCG GAA GCC ACA TAC TCT CCG TGC GGC TCC GGT CCC TGG ATT ACA CCC Pro Glu Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro 240 245 250	2988
AGG TGC ATG GTC GAC TAC CCG TAT AGG CTT TGG CAC TAT CCT TGT ACC Arg Cys Met Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr 255 260 265 270	3036
ATC AAT TAC ACC ATA TTC AAA GTC AGG ATG TAC GTG GGA GGG GTC GAG Ile Asn Tyr Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu 275 280 285	3084
CAC AGG CTG GAA GCG GCC TGC AAC TGG ACG CGG GGC GAA CGC TGT GAT His Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp 290 295 300	3132
CTG GAA GAC AGG GAC AGG TCC GAG CTC AGC CCG TTA CTG CTG TCC ACC Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Ser Thr 305 310 315	3180
ACG CAG TGG CAG GTC CTT CCG TGT TCT TTC ACG ACC CTG CCA GCC TTG Thr Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu 320 325 330	3228
TCC ACC GGC CTC ATC CAC CTC CAC CAG AAC ATT GTG GAC GTG CAG TAC Ser Thr Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr 335 340 345 350	3276
TTG TAC GGG GTA GGG TCA AGC ATC GCG TCC TGG GCT ATT AAG TGG GAG Leu Tyr Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu 355 360 365	3324
TAC GAC GTT CTC CTG TTC CTG CTT GCA GAC GCG CGC GTT TGC TCC Tyr Asp Val Leu Leu Phe Leu Leu Ala Asp Ala Arg Val Cys Ser 370 375 380	3372
TGC TTG TGG ATG ATG TTA CTC ATA TCC CAA GCG GAG GCG GCT TTG GAG Cys Leu Trp Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu 385 390 395	3420
AAC TAATCTAGAG GGCCCTATTC TATAGTGTCA CCTAAATGCT AGAGGATCTT Asn	3473

TGTGAAGGAA CCTTACTTCT GTGGTGTGAC ATAATTGGAC AACTACCTA CAGAGATTA	3533
AAGCTCTAAG GTAAATATAA AATTTTTAAG TGTATAATGT GTTAAACTAC TGATTCTAAT	3593
TGTTTGTGTA TTTAGATTC CAACCTATGG AACTGATGAA TGGGACCAAGT CGTGGAAATGC	3653
CTTTAATGAG GAAACCTGT TTTGCTCAGA AGAAATGCCA TCTAGTGATG ATGAGGCTAC	3713
TGCTGACTCT CAACATTCTA CTCCCTCCAAA AAAGAAGAGA AAGGTAGAAG ACCCCAAAGGA	3773
CTTTCCTCA GAATTGCTAA GTTTTTGAG TCATGCTGTG TTTAGTAATA GAACTCTTGC	3833
TTGCTTTGCT ATTTACACCA CAAAGGAAAA AGCTGCACTG CTATACAAGA AAATTATGGA	3893
AAAATATTCT GTAACCTTTA TAAGTAGGCA TAACAGTTAT AATCATAACA TACTGTTTT	3953
TCTTACTCCA CACAGGCATA GAGTGTCTGC TATTAATAAC TATGCTCAA AATTGTGTAC	4013
CTTTAGCTTT TTAATTGTA AAGGGGTTAA TAAGGAATAT TTGATGTATA GTGCCTTGAC	4073
TAGAGATCAT AATCAGCCAT ACCACATTG TAGAGGTTTT ACTTGCTTTA AAAAACCTCC	4133
CACACCTCCC CCTGAACCTG AAACATAAAA TGAATGCAAT TGTTGTTGTT AACTGTTTA	4193
TTGCAGCTTA TAATGGTTAC AAATAAGCA ATAGCATCAC AAATTTCACA AATAAAGCAT	4253
TTTTTCACT GCATTCTAGT TGTGGTTGT CCAAACTCAT CAATGTATCT TATCATGTCT	4313
GGATCGATCC CGCCATGGTA TCAACGCCAT ATTTCTATT ACAGTAGGGA CCTCTTCGTT	4373
GTGTAGGTAC CGCTGTATTC CTAGGGAAAT AGTAGAGGCA CCTTGAACTG TCTGCATCAG	4433
CCATATAGCC CCCGCTGTTG GACTTACAAA CACAGGCACA GTACTGACAA ACCCATAACAC	4493
CTCCTCTGAA ATACCCATAG TTGCTAGGGC TGTCTCCGAA CTCATTACAC CCTCCAAAGT	4553
CAGAGCTGTA ATTCGCCAT CAAGGGCAGC GAGGGCTCT CCAGATAAAA TAGCTCTGC	4613
CGAGAGTCCC GTAAGGGTAG ACACTTCAGC TAATCCCTCG ATGAGGTCTA CTAGAATAGT	4673
CAGTGCAGGCT CCCATTTGA AAATTCACTT ACTTGATCAG CTTCAAGAAGA TGGCGGAGGG	4733
CCTCCAACAC AGTAATTTC CTCCCGACTC TTAAAATAGA AAATGTCAAG TCAGTTAACG	4793
AGGAAGTGGG CTAACGTGACG CAGCTGGCCG TGGCACATCC TCTTTAATT AGTTGCTAGG	4853
CAACGCCCTC CAGAGGGCGT GTGGTTTGC AAGAGGAAGC AAAAGCCTCT CCACCCAGGC	4913
CTAGAATGTT TCCACCCAAT CATTACTATG ACAACAGCTG TTTTTTTAG TATTAAGCAG	4973
AGGCCGGGGA CCCCTGGCCC GCTTACTCTG GAGAAAAGA AGAGAGGCAT TGTAGAGGCT	5033
TCCAGAGGCA ACTTGCTAAA ACAGGACTGC TTCTATTCT GTCACACTGT CTGGCCCTGT	5093

CACAAGGTCC AGCACCTCCA TACCCCTTT AATAAGCAGT TTGGGAACGG GTGCGGGTCT	5153
TACTCCGCCA ATCCCGCCCC TAACTCCGCC CAGTTCCGCC CATTCTCCGC CCCATGGCTG	5213
ACTAATTTTT TTTATTTATG CAGAGGCCGA GGCCGCCCTCG GCCTCTGAGC TATTCCAGAA	5273
GTAGTGAGGA GGCTTTTTTG GAGGCCTAGG CTTTGCAAA AAGCTAATTC	5323

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 399 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu			
1	5	10	15

Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Ala Ala Ala Asn Ser		
20	25	30

Glu Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala Gly Leu		
35	40	45

Val Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu Ile Asn		
50	55	60

Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys Asn Glu			
65	70	75	80

Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe		
85	90	95

Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg Leu Thr		
100	105	110

Asp Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly Ser Gly		
115	120	125

Leu Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Pro Cys Gly		
130	135	140

Ile Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro			
145	150	155	160

Ser Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr Tyr		
165	170	175

Ser Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg		
180	185	190

Pro Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly
195 200 205

Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly Val Gly
210 215 220

Asn Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys His Pro Glu
225 230 235 240

Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg Cys
245 250 255

Met Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile Asn
260 265 270

Tyr Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu His Arg
275 280 285

Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu Glu
290 295 300

Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Ser Thr Thr Gln
305 310 315 320

Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala Leu Ser Thr
325 330 335

Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val Gln Tyr Leu Tyr
340 345 350

Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys Trp Glu Tyr Asp
355 360 365

Val Leu Leu Phe Leu Leu Ala Asp Ala Arg Val Cys Ser Cys Leu
370 375 380

Trp Met Met Leu Leu Ile Ser Gln Ala Glu Ala Ala Leu Glu Asn
385 390 395

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5125 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 2227..3225

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GCGTAATCTG CTGCTTGCAA ACAAAAAAAC CACCGCTACC AGCGGTGGTT TGTTTGCCGG	60
ATCAAGAGCT ACCAACTCTT TTTCCGAAGG TAACTGGCTT CAGCAGAGCG CAGATACCAA	120
ATACTGTCCT TCTAGTGTAG CCGTAGTTAG GCCACCACCT CAAGAACTCT GTAGCACCGC	180
CTACATACCT CGCTCTGCTA ATCCTGTTAC CAGTGGCTGC TGCCAGTGGC GATAAGTCGT	240
GTCTTACCGG GTTGGACTCA AGACGATAGT TACCGGATAA GGCCGACCGG TCGGGCTGAA	300
CGGGGGGTTTC GTGCACACAG CCCAGCTTGG AGCGAACGAC CTACACCGAA CTGAGATACC	360
TACAGCGTGA GCATTGAGAA AGCGCCACGC TTCCCGAAGG GAGAAAGGCG GACAGGTATC	420
CGGTAAGCGG CAGGGTCGGA ACAGGAGAGC GCACGAGGGG GCTTCCAGGG GGAAACGCCT	480
GGTATCTTTA TAGTCCTGTC GGGTTCGCC ACCTCTGACT TGAGCGTCGA TTTTTGTGAT	540
GCTCGTCAGG GGGCGGAGC CTATGGAAAA ACGCCAGCAA CGCAAGCTAG CTTCTAGCTA	600
GAAATTGTAA ACGTTAATAT TTTGTAAAA TTCGCGTTAA ATTTTGTAA AATCAGCTCA	660
TTTTTTAACC AATAGGCCGA AATCGGAAA ATCCCTTATA AATCAAAGA ATAGCCGAG	720
ATAGGGTTGA GTGTTGTTCC AGTTTGGAAC AAGAGTCCAC TATTAAAGAA CGTGGACTCC	780
AACGTCAAAG GCGAAAAAAC CGTCTATCAG GGCGATGGCC GCCCACTACG TGAACCATCA	840
CCCAAATCAA GTTTTTGGG GTCGAGGTGC CGTAAAGCAC TAAATCGGAA CCCTAAAGGG	900
AGCCCCCGAT TTAGAGCTTG ACGGGAAAG CCGCGAACG TGGCGAGAAA GGAAGGGAAG	960
AAAGCGAAAG GAGCGGGCGC TAGGGCGCTG GCAAGTGTAG CGGTACGCT GCGCGTAACC	1020
ACCACACCCG CCGCGCTTAA TGCGCCGCTA CAGGGCGCGT ACTATGGTTG CTTTGACGAG	1080
ACCGTATAAC GTGCTTTCT CGTTGGAATC AGAGCGGGAG CTAAACAGGA GGCGATTAA	1140
AGGGATTAA GACAGGAACG GTACGCCAGC TGGATCACCG CGGTCTTCT CAACGTAACA	1200
CTTTACAGCG GCGCGTCATT TGATATGATG CGCCCCGCTT CCCGATAAGG GAGCAGGCCA	1260
GTAAAAGCAT TACCCGTGGT GGGGTTCCCG AGCGGCCAAA GGGAGCAGAC TCTAAATCTG	1320
CCGTCATCGA CTTCGAAGGT TCGAATCCTT CCCCCACAC CATCACTTTC AAAAGTCCGA	1380
AAGAATCTGC TCCCTGCTTG TGTGTTGGAG GTCGCTGAGT AGTGCAGCAG TAAAATTAA	1440
GCTACAAACAA GGCAAGGCTT GACCGACAAT TGCATGAAGA ATCTGCTTAG GGTTAGGCGT	1500
TTTGCCTGTC TTGCGATGT ACGGGCCAGA TATACGCGTT GACATTGATT ATTGACTAGT	1560

TATTAATAGT AATCAATTAC GGGTCATTA GTTCATAGCC CATATATGGA GTTCCGCGTT	1620
ACATAACTTA CGGTAAATGG CCCGCCTGGC TGACCGCCCA ACGACCCCCG CCCATTGACG	1680
TCAATAATGA CGTATGTTCC CATAGTAACG CCAATAGGGA CTTTCCATTG ACGTCAATGG	1740
GTGGACTATT TACGGTAAAC TGCCCACTTG GCAGTACATC AAGTGTATCA TATGCCAAGT	1800
ACGCCCCCTA TTGACGTCAA TGACGGTAAA TGGCCCGCCT GCCATTATGC CCAGTACATG	1860
ACCTTATGGG ACTTTCCTAC TTGGCAGTAC ATCTACGTAT TAGTCATCGC TATTACCATG	1920
GTGATGCGGT TTTGGCAGTA CATCAATGGG CGTGGATAGC GGTTTGACTC ACGGGGATTT	1980
CCAAGTCTCC ACCCCATTGA CGTCAATGGG AGTTTGTTTT GGCACCAAAA TCAACGGGAC	2040
TTTCCAAAAT GTCGTAACAA CTCCGCCCCA TTGACGCAA TGGCGGTAG GCGTGTACGG	2100
TGGGAGGTCT ATATAAGCAG AGCTCTCTGG CTAACTAGAG AACCCACTGC TTAACTGGCT	2160
TATCGAAATT AATACGACTC ACTATAAGGA GACCGGAAGC TTGGTACCGA GCTCGGATCT	2220
GCCACC ATG GCA ACA GGA TCA AGA ACA TCA CTG CTG CTG GCA TTT GGA	2268
Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly	
1 5 10	
CTG CTG TGT CTG CCA TGG CTG CAA GAA GGA TCA GCA GCA GCA GCG	2316
Leu Leu Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Ala Ala Ala Ala	
15 20 25 30	
AAT TCA GAA ACC CAC GTC ACC GGG GGA AGT GCC GGC CAC ACC ACG GCT	2364
Asn Ser Glu Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala	
35 40 45	
GGG CTT GTT CGT CTC CTT TCA CCA GGC GCC AAG CAG AAC ATC CAA CTG	2412
Gly Leu Val Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu	
50 55 60	
ATC AAC ACC AAC GGC AGT TGG CAC ATC AAT AGC ACG GCC TTG AAC TGC	2460
Ile Asn Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys	
65 70 75	
AAT GAA AGC CTT AAC ACC GGC TGG TTA GCA GGG CTC TTC TAT CAC CAC	2508
Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His	
80 85 90	
AAA TTC AAC TCT TCA GGT TGT CCT GAG AGG TTG GCC AGC TGC CGA CGC	2556
Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg	
95 100 105 110	
CTT ACC GAT TTT GCC CAG GGC GGG GGT CCT ATC AGT TAC GCC AAC GGA	2604
Leu Thr Asp Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly	
115 120 125	
AGC GGC CTC GAT GAA CGC CCC TAC TGC TGG CAC TAC CCT CCA AGA CCT	2652

GTAAATATAA AATTTTTAAG TGTATAATGT GTTAAACTAC TGATTCTAAT TGTTTGTGTA	3405
TTTTAGATTC CAACCTATGG AACTGATGAA TGGGAGCAGT GGTGGAATGC CTTTAATGAG	3465
GAAAACCTGT TTTGCTCAGA AGAAATGCCA TCTAGTGATG ATGAGGCTAC TGCTGACTCT	3525
CAACATTCTA CTCCCTCCAAA AAAGAAGAGA AAGGTAGAAG ACCCCAAGGA CTTTCCCTCA	3585
GAATTGCTAA GTTTTTGAG TCATGCTGTG TTTAGTAATA GAACTCTTGC TTGCTTGCT	3645
ATTTACACCA CAAAGGAAAA AGCTGCCTTG CTATACAAGA AAATTATGGA AAAATATTCT	3705
GTAAACCTTA TAAGTAGGCA TAACAGTTAT AATCATAACA TACTGTTTT TCTTACTCCA	3765
CACAGGCATA GAGTGTCTGC TATTAATAAC TATGCTAAA AATTGTGTAC CTTTAGCTTT	3825
TTAATTGTA AAGGGGTTAA TAAGGAATAT TTGATGTATA GTGCCTTGAC TAGAGATCAT	3885
AATCAGCCAT ACCACATTG TAGAGTTTT ACTTGCTTTA AAAAACCTCC CACACCTCCC	3945
CCTGAACCTG AAACATAAAA TGAATGCAAT TGTTGTTGTT AACTTGTTA TTGCAGCTTA	4005
TAATGGTTAC AAATAAAGCA ATAGCATCAC AAATTCACA AATAAAGCAT TTTTTCACT	4065
GCATTCTAGT TGTGGTTTGT CCAAACTCAT CAATGTATCT TATCATGTCT GGATCGATCC	4125
CGCCATGGTA TCAACGCCAT ATTTCTATTT ACAGTAGGGA CCTCTTCGTT GTGTAGGTAC	4185
CGCTGTATTG CTAGGGAAAT AGTAGAGGCA CCTTGAAC TG TCTGCATCAG CCATATAGCC	4245
CCCGCTGTTG GACTTACAAA CACAGGCACA GTACTGACAA ACCCATAACAC CTCCTCTGAA	4305
ATACCCATAG TTGCTAGGGC TGTCTCCGAA CTCATTACAC CCTCCAAAGT CAGAGCTGTA	4365
ATTTCGCCAT CAAGGGCAGC GAGGGCTTCT CCAGATAAAA TAGCTTCTGC CGAGAGTCCC	4425
GTAAGGGTAG ACACCTCAGC TAATCCCTCG ATGAGGTCTA CTAGAATAGT CAGTGCCTGCT	4485
CCCATTTGA AAATTCACCTT ACTTGATCAG CTTCAGAAGA TGGCGGAGGG CCTCCAACAC	4545
AGTAATTTCCTCCTC TTAAAATAGA AAATGTCAAG TCAGTTAACG AGGAAGTGGA	4605
CTAACTGACG CAGCTGGCCG TGCGACATCC TCTTTTAATT AGTTGCTAGG CAACGCCCTC	4665
CAGAGGGCGT GTGGTTTGCA AAGAGGAAGC AAAAGCCTCT CCACCCAGGC CTAGAATGTT	4725
TCCACCCAAAT CATTACTATG ACAACAGCTG TTTTTTTAG TATTAAGCAG AGGCCGGGGA	4785
CCCCTGGCCC GCTTACTCTG GAGAAAAAGA AGAGAGGCAT TGTAGAGGCT TCCAGAGGCA	4845
ACTTGTCATAAA ACAGGACTGC TTCTATTCT GTCACACTGT CTGGCCCTGT CACAAGGTCC	4905
AGCACCTCCA TACCCCTTT AATAAGCAGT TTGGGAACGG GTGCAGGTCT TACTCCGCC	4965
ATCCCAGCCCC TAATCCGCC CAGTTCCGCC CATTCTCCGC CCCATGGCTG ACTAATT	5025

TTTATTTATG CAGAGGCCGA GGCGCCCTCG GCCTCTGAGC TATTCCAGAA GTAGTGAGGA	5085
GGCTTTTTTG GAGGCCTAGG CTTTTGCAAA AAGCTAATTG	5125

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 333 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Ala Thr Gly Ser Arg Thr Ser Leu Leu Leu Ala Phe Gly Leu Leu
 1 5 10 15

Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala Ala Ala Ala Asn Ser
 20 25 30

Glu Thr His Val Thr Gly Gly Ser Ala Gly His Thr Thr Ala Gly Leu
 35 40 45

Val Arg Leu Leu Ser Pro Gly Ala Lys Gln Asn Ile Gln Leu Ile Asn
 50 55 60

Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu Asn Cys Asn Glu
 65 70 75 80

Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr His His Lys Phe
 85 90 95

Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Arg Leu Thr
 100 105 110

Asp Phe Ala Gln Gly Gly Pro Ile Ser Tyr Ala Asn Gly Ser Gly
 115 120 125

Leu Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Pro Cys Gly
 130 135 140

Ile Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro
 145 150 155 160

Ser Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr Tyr
 165 170 175

Ser Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu Asn Asn Thr Arg
 180 185 190

Pro Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly
 195 200 205

Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly Val Gly
210 215 220

Asn Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys His Pro Glu
225 230 235 240

Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg Cys
245 250 255

Met Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile Asn
260 265 270

Tyr Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly Val Glu His Arg
275 280 285

Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg Cys Asp Leu Glu
290 295 300

Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Ser Thr Thr Gln
305 310 315 320

Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro Ala
325 330

WHAT IS CLAIMED IS:

1. Plasmid pHCV-162.
2. Plasmid pHCV-167.
3. Plasmid pHCV-168.
- 5 4. Plasmid pHCV-169.
- 5 5. Plasmid pHCV-170.
6. APP-HCV-E2 fusion protein expressed by a mammalian expression vector pHCV-162.
- 10 7. APP-HCV-E2 fusion protein expressed by a mammalian expression vector pHCV-167.
8. HGH-HCV-E2 fusion protein expressed by a mammalian expression vector pHCV-168.
- 15 9. HGH-HCV-E2 fusion protein expressed by a mammalian expression vector pHCV-169.
10. HGH-HCV-E2 fusion protein expressed by a mammalian expression vector pHCV-170.
- 20 11. A method for detecting HCV antigen or antibody in a test sample suspected of containing HCV antigen or antibody, wherein the improvement comprises contacting the test sample with a glycosylated HCV antigen produced in a mammalian expression system.
- 20 12. A method for detecting HCV antigen or antibody in a test sample suspected of containing HCV antigen or antibody, wherein the improvement comprises contacting the test sample with an antibody produced by using a glycosylated HCV antigen produced in a mammalian expression system.
- 25 13. The method of claim 12 wherein said antibody is a monoclonal antibody.
14. The method of claim 12 wherein said antibody is a polyclonal antibody.
15. A test kit for detecting the presence of HCV antigen or HCV antigen in a test sample suspected of containing said HCV antigen or antibody, comprising:
30 a container containing a glycosylated HCV antigen produced in a mammalian expression system.
- 35 16. The test kit of claim 15 further comprising an antibody produced by using a glycosylated HCV antigen produced in a mammalian expression system.

17. A test kit for detecting the presence of HCV antigen or HCV antibody in a test sample suspected of containing said HCV antigen or HCV antibody, comprising:

5 a container containing an antibody produced by using a glycosylated HCV antigen produced in a mammalian expression system.

18. The test kit of claim 17 wherein said antibody is a polyclonal antibody.

19. The test kit of claim 17 wherein said antibody is a monoclonal antibody.

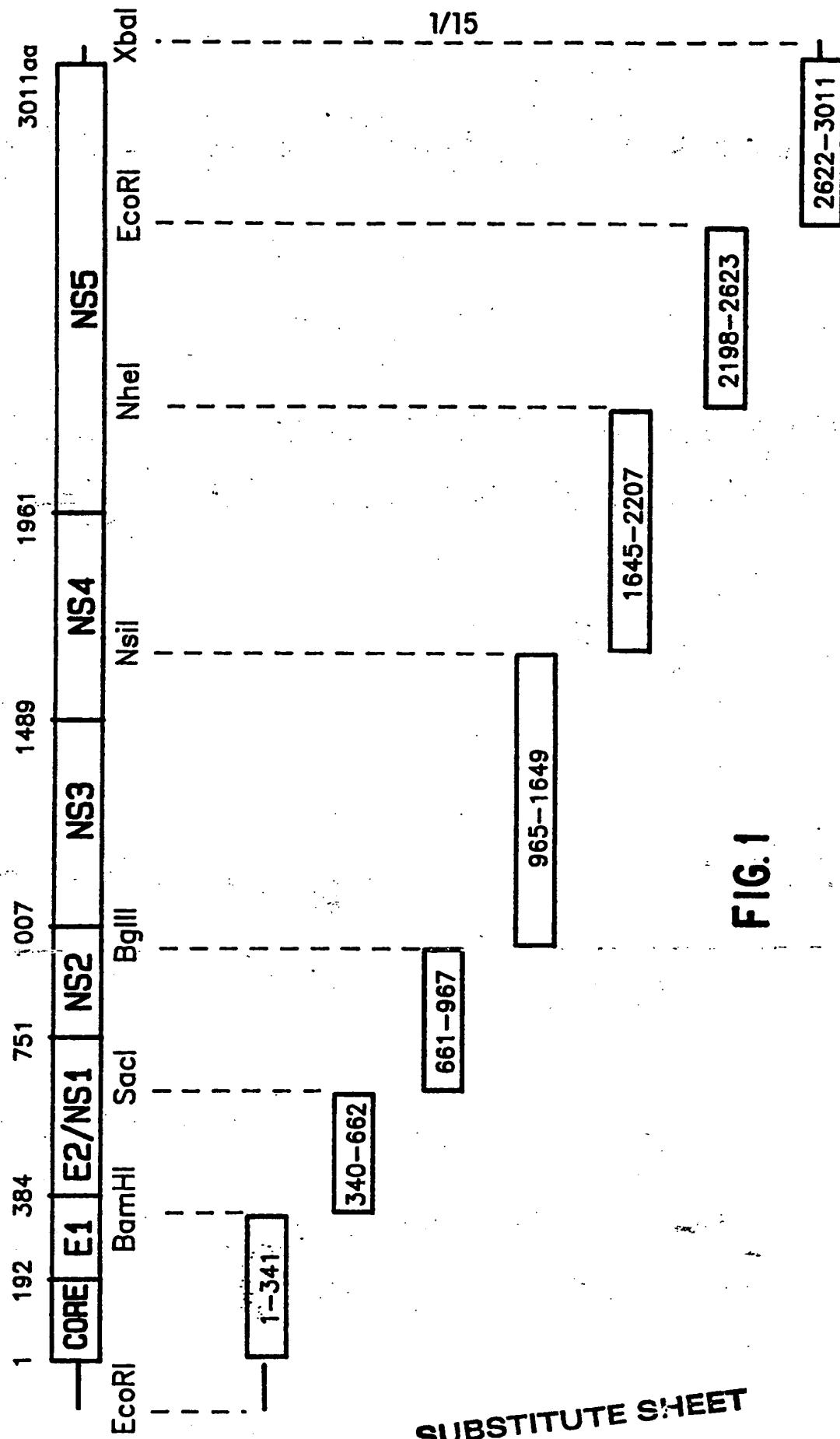
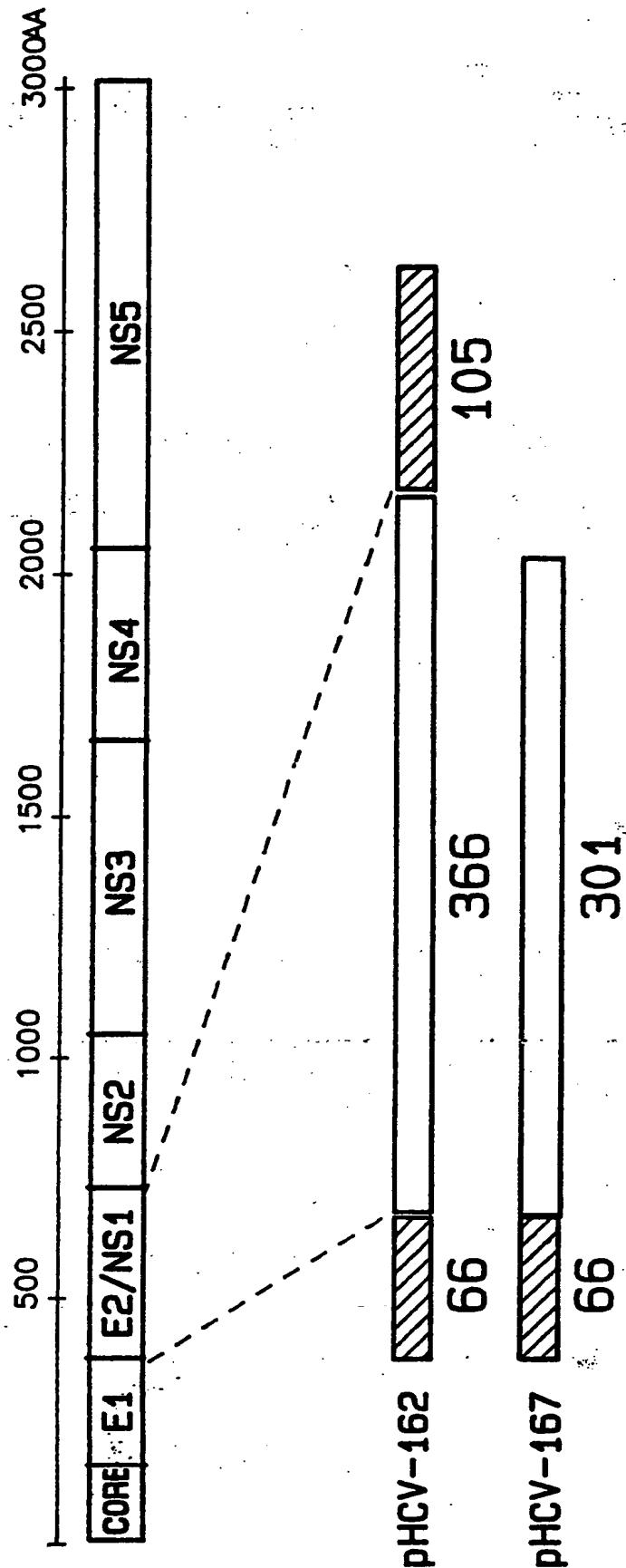


FIG. 1

SUBSTITUTE SHEET

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**SUBSTITUTE SHEET**

HCV AA# 384-749 or
HCV AA# 384-684
FUSION TO APP PROTEIN
CMV PROMOTER
HEK CELLS

FIG.2

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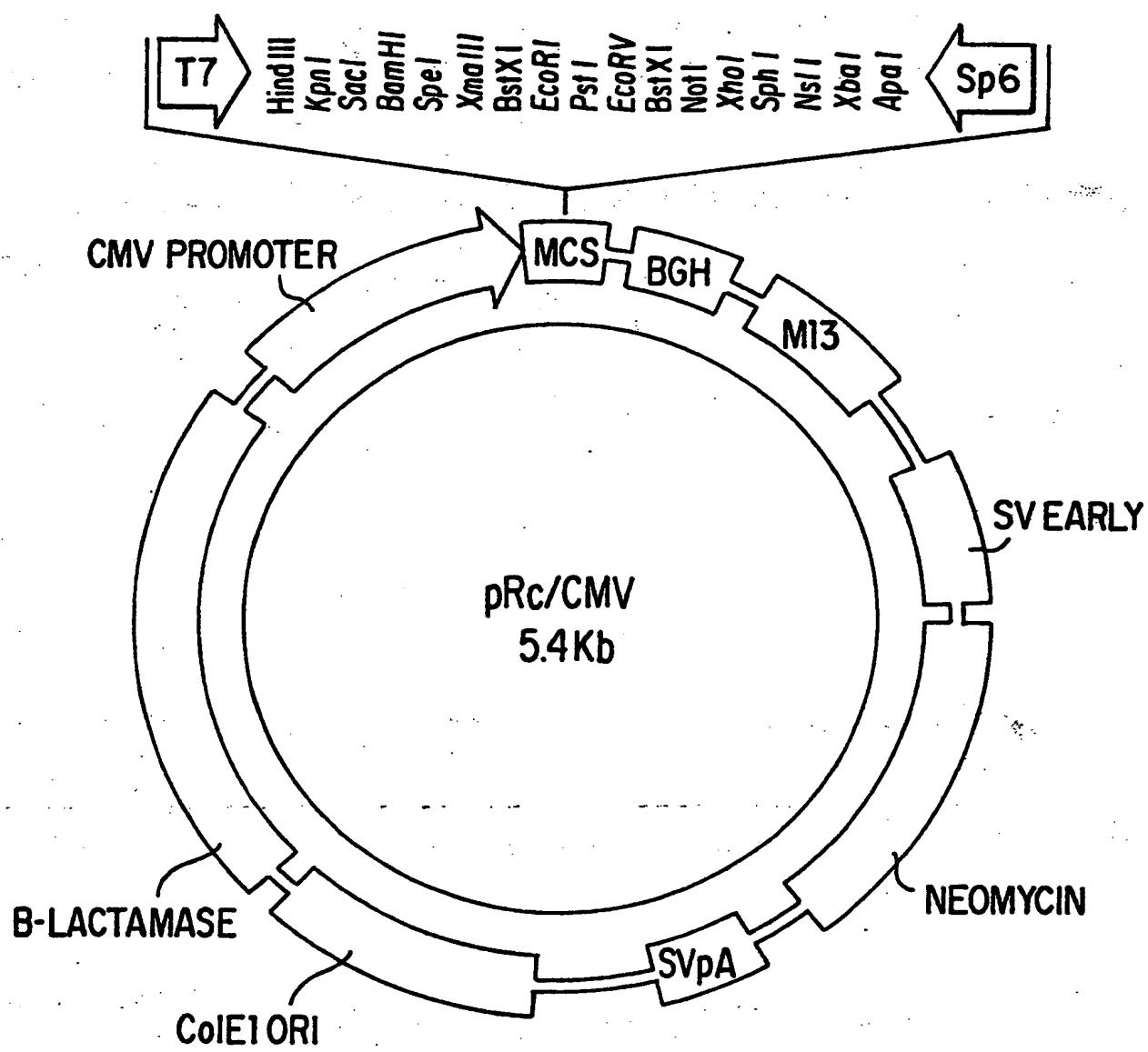


FIG. 3

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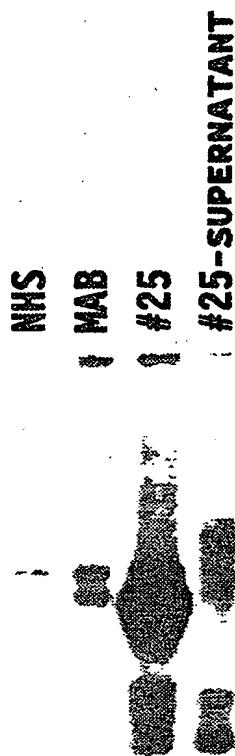


FIG. 4

SUBSTITUTE SHEET

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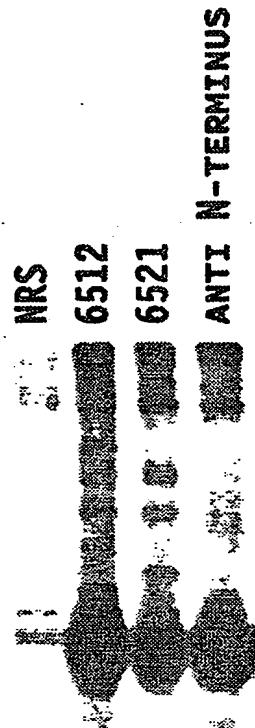


FIG. 5

SUBSTITUTE SHEET

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NHS	P	HCV167
#25	L	YSATE
NHS	P	HCV167
#25	S	UPERNATANT



FIG. 6

SUBSTITUTE SHEET

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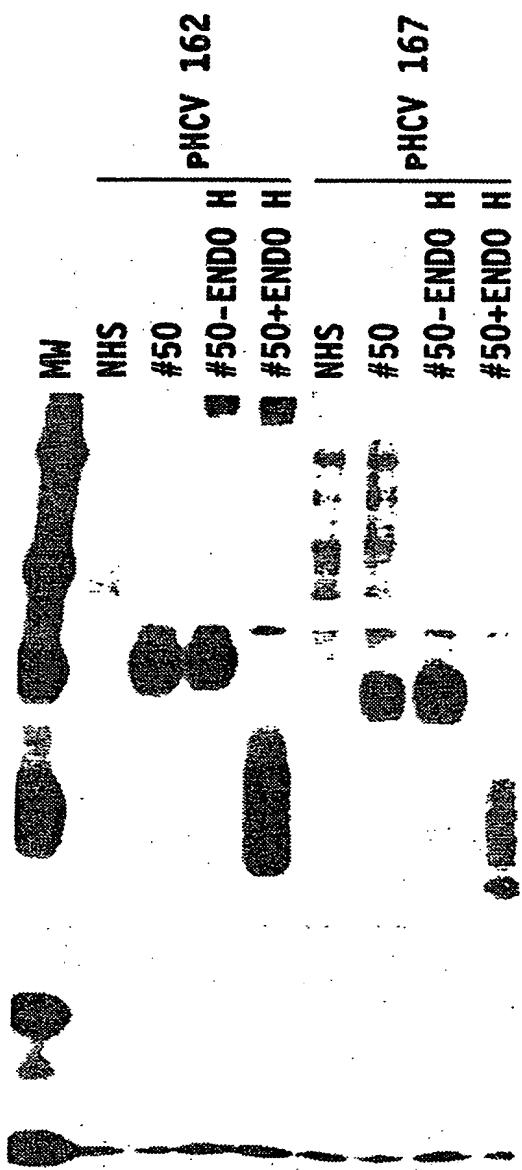


FIG. 7

SUBSTITUTE SHEET

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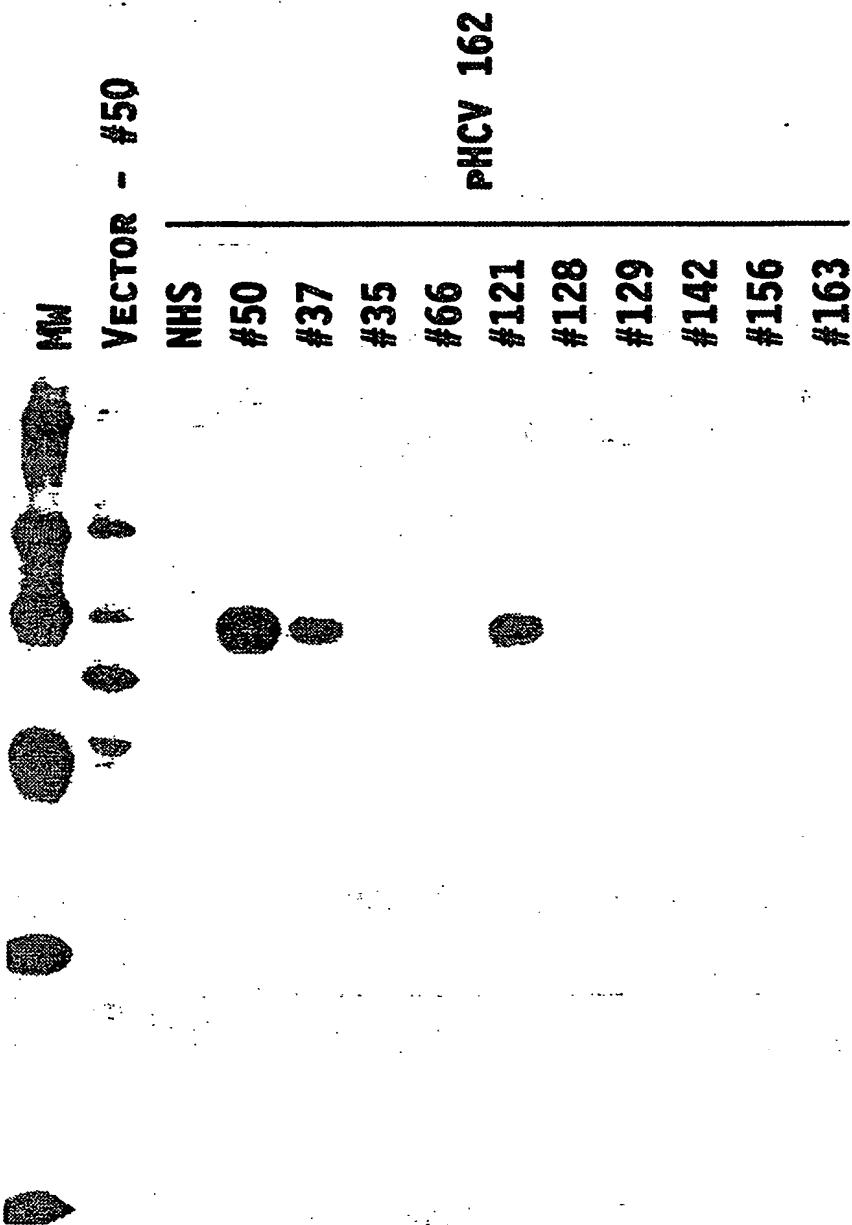


FIG. 8

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MW
#50
410
435
441
476
496
560
589
620
622
623
633
639
641
648
649
657
666
672

FIG. 9

SUBSTITUTE SHEET

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!	0	1	2	3	4	5	6	7	8	9	MW
											#50
											673
											677
											694
											696
											706
											717
											728
											740
											743

FIG. 10

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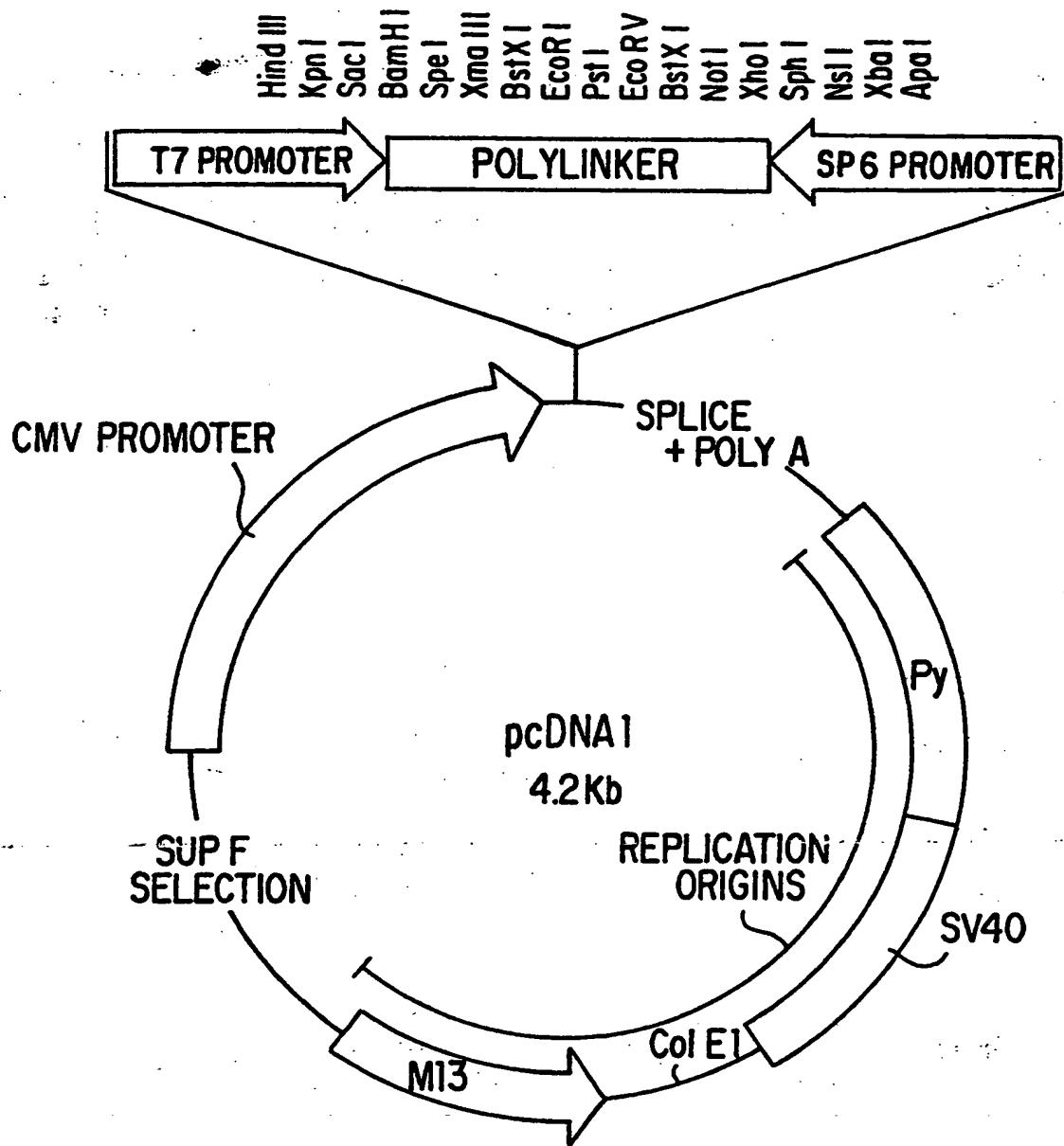
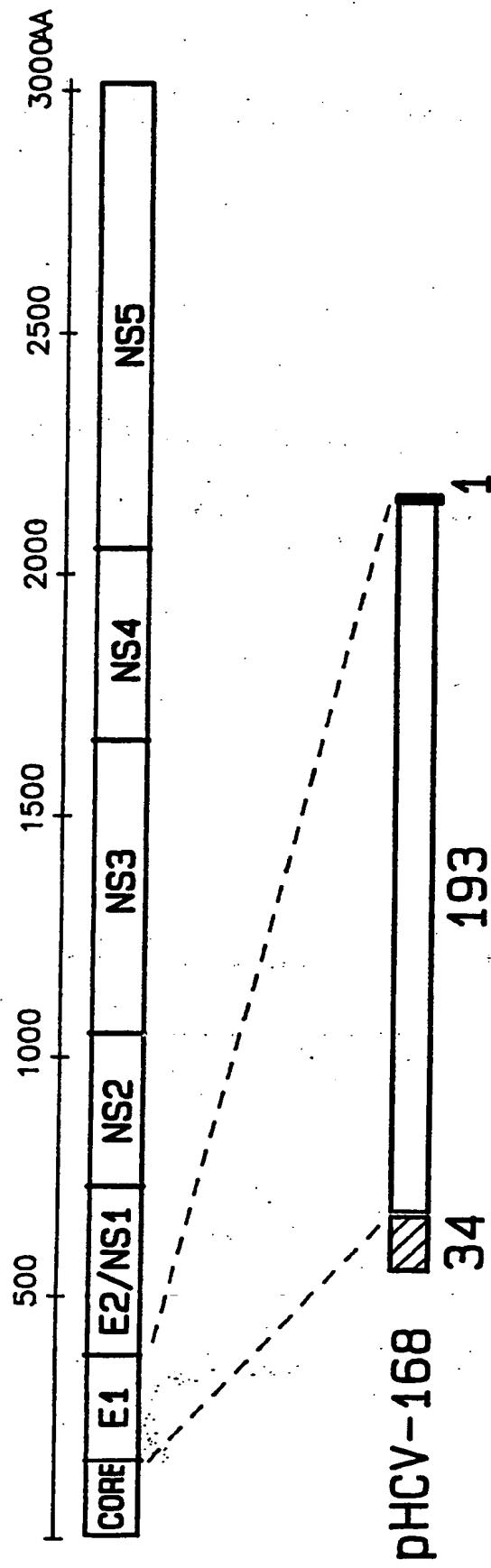


FIG. 11

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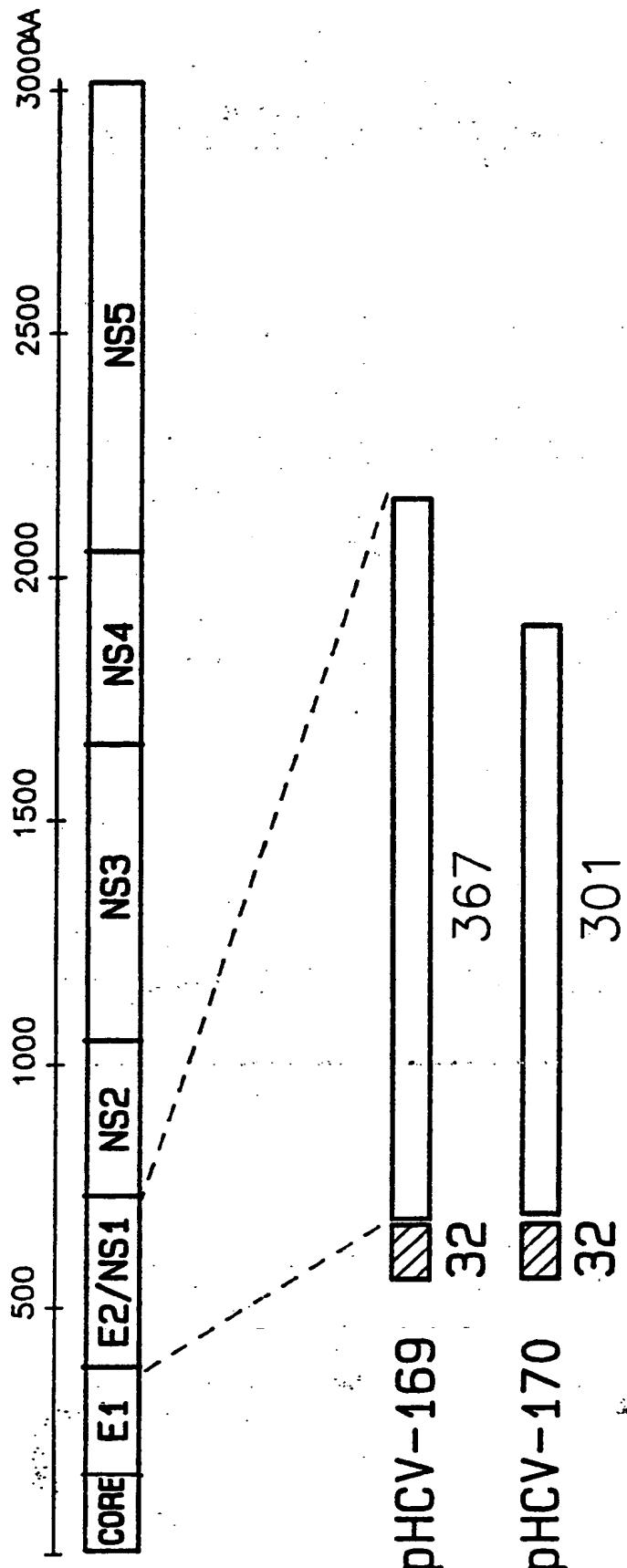


HCV AA# 192-384
HGH SECRETION SIGNAL
CMV PROMOTER
HEK CELLS

FIG. 12

SUBSTITUTE SHEET

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HCV AA# 384-750 or
HCV AA# 384-684
HGH SECRETION SIGNAL
CMV PROMOTER
HEK CELLS

SUBSTITUTE SHEET

FIG. 13

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PHCV 168
LYSATE

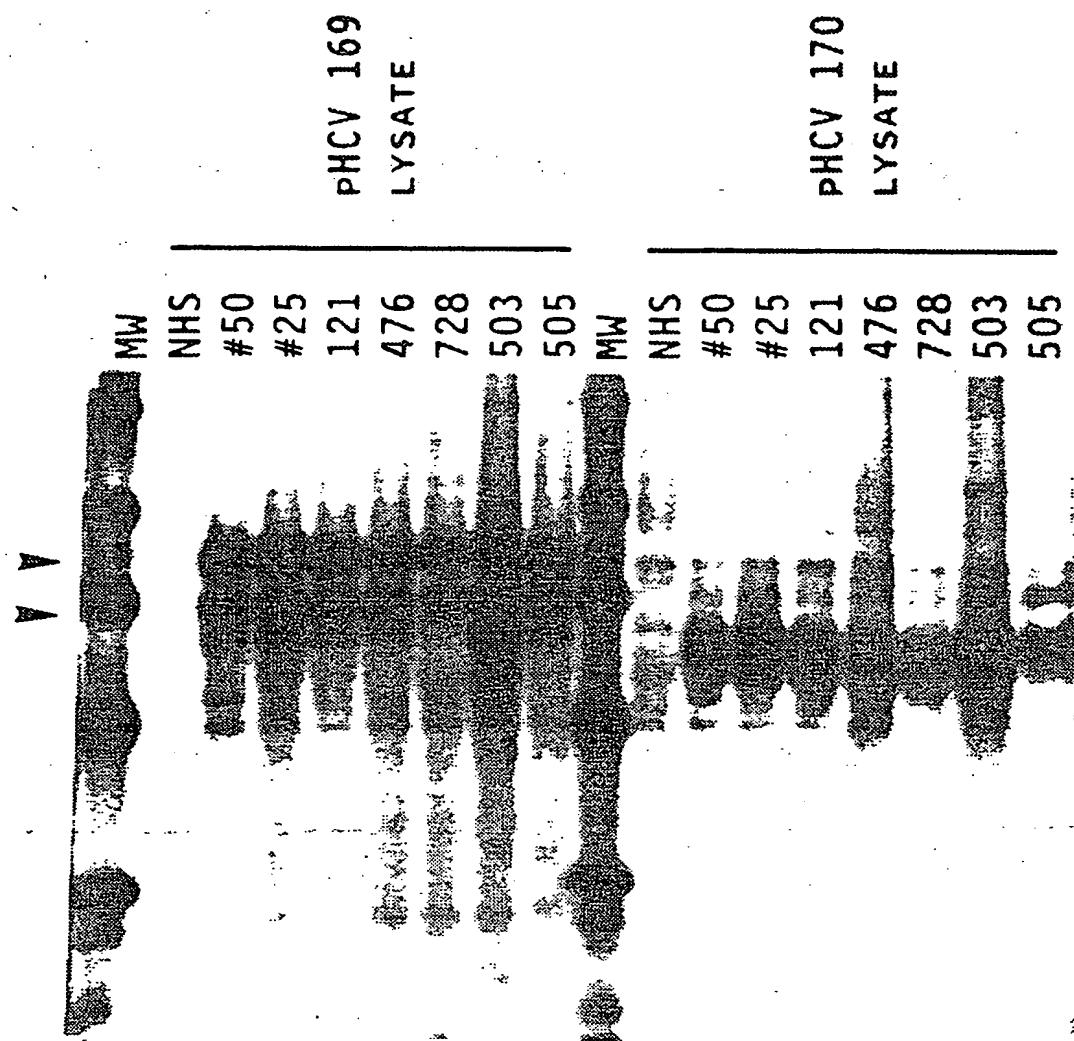
MW NHS #50 #25 121 476 728 503 505



FIG. 14

SUBSTITUTE SHEET

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SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00907

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C12N 15/00; C12Q 1/70; C07K 15/00
US CL :435/320.1, 5; 530/409

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/320.1, 69.3, 5, 7.1; 530/350, 409

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PIR, SWISS-PROT, GENESEQ, GENBANK, WPI, CA, MEDLINE, APS

search terms: hepatitis C virus, HCV, fusion, amyloid precursor protein, human growth hormone, diagnos?, kit

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Proceedings of the National Academy of Sciences USA, Volume 88, issued March 1991. Q.-L. Choo et al, "Genetic Organization and Diversity of the Hepatitis C Virus", pp. 2451-2455, see entire document.	1-18
Y	Journal of General Virology, Volume 72, issued October 1991, D. Kremsdorff et al., "Partial Nucleotide Sequence Analysis of a French Hepatitis C Virus: Implications for HCV Variability in the E2/NS1 Protein", pp. 2557-2561, see entire document.	1-18

<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
"A" document defining the general state of the art which is not considered to be part of particular relevance		"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date		"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means			
"P" document published prior to the international filing date but later than the priority date claimed			

Date of the actual completion of the international search

30 April 1993

Date of mailing of the international search report

11 MAY 1993

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

D. BARND

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/00907

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Virology, Volume 65, No. 3, issued March 1991, A. Takamizawa et al., "Structure and Organization of the Hepatitis C Virus Genome Isolated from Human Carriers", pp. 1105-1113, see entire document.	1-18
Y	Proceedings of the National Academy of Sciences USA, Volume 87, issued December 1990, N. Kato et al., "Molecular Cloning of the Human Hepatitis C Virus Genome from Japanese Patients with non-A, non-B Hepatitis", pp. 9524-9528, see entire document.	1-18
Y	Journal of General Virology, Volume 72, issued November 1991, H. Okamoto et al., "Nucleotide Sequence of the Genomic RNA of Hepatitis C Virus Isolated from a Human Carrier: Comparison with Reported Isolates for Conserved and Divergent Regions", pp. 2697-2704, see entire document.	1-18
Y	Gene, Volume 105, No. 2, issued 1991, J. Li et al., "Two French Genotypes of Hepatitis C Virus: Homology of the Predominant Genotype with the Prototype American Strain", pp. 167-172, see entire document.	1-18
Y,P	US, A, 5,106,726 (Wang) 21 April 1992, see entire document.	1-18
Y	EP, A, 0,318,216 (Houghton et al) 31 May 1989, see entire document.	1-18
Y	EP, A, 0,388,232 (Houghton et al) 19 September 1990, see entire document.	1-18
Y	GB, A, 2,212,511 (Houghton et al) 26 July 1989, see entire document.	1-18
Y	Cell, Volume 57, No. 1, issued 07 April 1989, A. Weidemann et al., "Identification, Biogenesis, and Localization of Precursors of Alzheimer's Disease A4 Amyloid Protein", pp. 115-126, see entire document.	1,2,6,7,11-18
Y	The Journal of Biological Chemistry, Volume 266, No. 29, issued 15 October 1991, D. E. Lowery et al., "Alzheimer's Amyloid Precursor Protein Produced by Recombinant Baculovirus Expression", pp. 19842-19850, see entire document.	1,2,6,7,11-18
Y	Vaccine, Volume 9, No. 8, issued August 1991, M. Kit et al., "Bovine Herpesvirus-1 (Infectious Bovine Rhinotracheitis Virus)-Based Viral Vector which Expresses Foot-and-Mouth Disease Epitopes", pp. 564-572, see entire document.	3-5,8-18